SUPPLEMENTARY APPENDIX

Bach RG, Cannon CP, Giugliano RP, et al. Benefit of simvastatin-ezetimibe compared with simvastatin monotherapy after acute coronary syndrome among patients 75 years or older: a secondary analysis of a randomized clinical trial. *JAMA Cardiol*. Published online July 17, 2019. doi:10.1001.jamacardio.2019.2306

IMPROVE-IT Protocol

Protocol for: Cannon CP, Blazing MA, Giugliano RP, et al. Ezetimibe added to statin therapy after acute coronary syndromes. N Engl J Med 2015;372:2387-97. DOI: 10.1056/NEJMoa1410489

This protocol supplement contains the following items:

1) Redacted final protocol
2) Redacted final statistical analysis plan and statistical amendment memo

Merck's policy on posting of redacted study protocols on journal websites is described in Merck Guidelines for Publication of Clinical Trials in the Scientific Literature on the www.merck.com website.

For publicly posted protocols, Merck redacts the background and rationale sections because these sections may contain proprietary information. Merck also redacts the names of any individuals due to privacy issues. The appendices generally are not provided because they may be lengthy and contain non-essential information. The publicly posted protocol includes all the key sections that are relevant to evaluating the study, specifically those sections describing the study objectives and hypotheses, the patient inclusion and exclusion criteria, the study design and procedures, the efficacy and safety measures, the statistical analysis plan, and amendments relating to those sections.

This report may include approved and non-approved uses, formulations, or treatment regimens. The results reported may not reflect the overall profile of a product. Before prescribing any product mentioned this report, healthcare professionals should consult local prescribing information for the product approved in their country.

1.0 TITLE PAGE

06 MAY 2005 - FINAL
19 APR 2007 – AMENDMENT #1
20 SEP 2007 - AMENDMENT #2
30 APR 2008 - AMENDMENT #3
There was no Amendment #4 implemented by the Sponsor. All changes to the trial since Amendment #3 are contained in this Amendment #5.
22 JUN 2011 - AMENDMENT #5

C O N F I D E N T I A L
STUDY PROTOCOL

SPONSOR:	Schering-Plough Research Institute, a Division of Schering Corporation 2015 Galloping Hill Road Kenilworth, NJ 07033 on behalf of MSP Singapore Company, LLC
STUDY TITLE:	A Multicenter, Double-Blind, Randomized Study to Establish the Clinical Benefit and Safety of Vytorin (Ezetimibe/Simvastatin Tablet) vs Simvastatin Monotherapy in High-Risk Subjects Presenting With Acute Coronary Syndrome (IMProved Reduction of Outcomes: Vytorin Efficacy International Trial – IMPROVE IT)
PROTOCOL NO.:	P04103
IND NO.:	65066
SCH NO.:	465981
EUDRACT NO.:	2005-001059-39
DOC ID:	***5641486***
TRIAL PHYSICIAN/DIRECTOR:	Redacted

2.0 SYNOPSIS

Title of Study: A Multicenter, Double-Blind, Randomized Study to Establish the Clinical Benefit and Safety of Vytorin (Ezetimibe/Simvastatin Tablet) vs Simvastatin Monotherapy in High-Risk Subjects Presenting With Acute Coronary Syndrome (IMProved Reduction of Outcomes: Vytorin Efficacy International Trial – IMPROVE IT) (Protocol No. P04103)

EUDRACT Number: 2005-001059-39

Study Centers: Up to 1500, worldwide

Duration of Study: Minimum: 48 months

Clinical Phase: 3b

Rationale: Redacted

Objectives: See **Synopsis Table 1** for a description of composite endpoint organization.

1. **Primary Objective: To evaluate the clinical benefit of treatment on Cardiovascular (CV) Death, Major Coronary Events, and Stroke:**

   The primary objective of this study is to evaluate the clinical benefit of Ezetimibe/Simvastatin Combination (single tablet containing ezetimibe and simvastatin) compared with simvastatin in stabilized acute coronary syndrome (ACS) subjects – either acute myocardial infarction (MI) or unstable angina. Clinical benefit will be defined as the reduction in the risk of the occurrence of the composite endpoint of CV death, major coronary events, and non-fatal stroke. CV death, major coronary events, and non-fatal stroke are designated primary endpoint events. Major coronary events include non-fatal MI, documented unstable angina that requires admission into a hospital, and all coronary revascularization with either percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) occurring at least 30 days after randomized treatment assignment. Only revascularization events that occur after the first 30 days of treatment will be considered as clinical endpoint events, in order to focus on revascularization events that can be reasonably expected to be affected by treatment and are unrelated to the initial ACS event.

2. **Secondary Objectives: To evaluate Supportive Composite Endpoints:**

   a. To evaluate the clinical benefit of Ezetimibe/Simvastatin Combination compared with simvastatin in stabilized ACS subjects on the occurrence of the composite endpoint of death due to all causes, major coronary events, and non-fatal stroke.

   b. To evaluate the clinical benefit of Ezetimibe/Simvastatin Combination compared with simvastatin in stabilized ACS subjects on the occurrence of the composite endpoint of death due to coronary heart disease (CHD) (CHD death), non-fatal MI, and urgent coronary revascularization with either PCI or CABG occurring at least 30 days after randomization.

   c. To evaluate the clinical benefit of Ezetimibe/Simvastatin Combination compared with simvastatin in stabilized ACS subjects on the composite endpoint of CV death, non-fatal MI, documented unstable angina that requires admission into a hospital, all revascularization (including both coronary and non-coronary) occurring at least 30 days after randomization, and non-fatal stroke.

3. **Tertiary Objectives:**

   a. **To evaluate the clinical benefit of treatment on Individual Endpoints:**

      To evaluate the clinical benefit of Ezetimibe/Simvastatin Combination compared with simvastatin in stabilized ACS subjects on each of the following endpoints analyzed individually: death from any cause, CHD death, CV death, MI, documented unstable angina that requires admission into a hospital, all coronary revascularization with either PCI or CABG occurring at least 30 days after randomization, urgent coronary revascularization with either PCI or CABG occurring at least 30 days after randomization, all revascularization (including both coronary and non-coronary) occurring at least 30 days after randomization, stroke, any cardiovascular event leading to admission into a hospital, and congestive heart failure (CHF) that requires hospitalization occurring at least 30 days after randomization.

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b. To evaluate the proportion of subjects achieving reductions in LDL-C and hs-CRP:

(1) To evaluate the percentage of subjects achieving endpoint concentrations for both LDL-C of <70 mg/dL (<1.8 mmol/L) and high-sensitivity C-Reactive Protein (hs-CRP) of <2.0 mg/L following 1 month and 4 months of treatment with Ezetimibe/Simvastatin Combination compared with simvastatin.

(2) To evaluate the potential relationship between the risk of occurrence of any primary endpoint event and the concentrations of LDL-C and high sensitivity-C-reactive protein (hs-CRP) following 1 month and 4 months of treatment with Ezetimibe/Simvastatin Combination or simvastatin.

c. To evaluate safety measurements:

To evaluate the safety and tolerability of Ezetimibe/Simvastatin Combination compared with simvastatin.

Hypotheses:

1. Primary Hypothesis: To evaluate the clinical benefit of treatment on CV Death, Major Coronary Events, and Stroke:

In stabilized high-risk ACS subjects, the administration of Ezetimibe/Simvastatin Combination compared with simvastatin will reduce the incidence of the composite endpoint of CV death, major coronary events (non-fatal MI, documented unstable angina that requires admission into a hospital, and all coronary revascularization with either PCI or CABG occurring at least 30 days after randomized treatment assignment), and non-fatal stroke.

2. Secondary Hypotheses: To evaluate Supportive Composite Endpoints:

a. In stabilized high-risk ACS subjects, the administration of Ezetimibe/Simvastatin Combination compared with simvastatin will reduce the incidence of the composite endpoint of death due to all causes, major coronary events, and non-fatal stroke.

b. In stabilized high-risk ACS subjects, the administration of Ezetimibe/Simvastatin Combination compared with simvastatin will reduce the incidence of the composite endpoint of CHD death, non-fatal MI, and urgent coronary revascularization with either PCI or CABG occurring at least 30 days after randomization.

c. In stabilized high-risk ACS subjects, the administration of Ezetimibe/Simvastatin Combination compared with simvastatin will reduce the incidence of the composite endpoint of CV death, non-fatal MI, documented unstable angina that requires admission into a hospital, all revascularization (including both coronary and non-coronary) occurring at least 30 days after randomization, and non fatal stroke.

3. Tertiary Hypotheses:

a. **To evaluate the clinical benefit of treatment on Individual Endpoints:**

In stabilized high-risk ACS subjects, the administration of Ezetimibe/Simvastatin Combination compared with simvastatin will reduce the incidence of the following endpoints, each analyzed individually: death from any cause, CHD death, CV death, MI, documented unstable angina that requires admission into a hospital, all coronary revascularization with either PCI or CABG occurring at least 30 days after randomization, urgent coronary revascularization with either PCI or CABG occurring at least 30 days after randomization, all revascularization (including both coronary and non-coronary) occurring at least 30 days after randomization, stroke, any cardiovascular event leading to admission into a hospital, and CHF that requires hospitalization occurring at least 30 days after randomization.

b. **To evaluate the proportion of subjects achieving reductions in LDL-C and hs-CRP:**

(1) In stabilized high-risk ACS subjects, the administration of Ezetimibe/Simvastatin Combination compared with simvastatin will result in a greater percentage of subjects achieving both an LDL-C concentration of <70 mg/dL (<1.8 mmol/L) and hs-CRP concentration of <2.0 mg/L.

(2) In stabilized high-risk ACS subjects, the group of subjects, regardless of treatment, achieving the dual goal of an LDL-C concentration of <70 mg/dL (<1.8 mmol/L) and an hs-CRP concentration of <2.0 mg/L will reduce the incidence of the primary composite endpoint compared with the group of subjects, regardless of

treatment, that do not achieve the dual goal for LDL-C and hs-CRP. **c. To evaluate safety measurements:**

In stabilized high-risk ACS subjects, Ezetimibe/Simvastatin Combination will be well-tolerated.

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Methodology: This study is to be conducted in conformance with Good Clinical Practices.

Subject Population: This is a multicenter, randomized, double-blind, active-control study of subjects with stabilized high-risk ACS and an LDL-C 125 mg/dL (3.2 mmol/L) (or 100 mg/dL [2.6 mmol/L] while receiving statin therapy) 10 days (240 hours) of admittance into a hospital.

The study will enroll ***approximately*** 18,000 high-risk subjects with STEMI or NSTE-ACS (unstable angina or NSTEMI).

With this Amendment #***5***, enrollment of new subjects ***has completed.***

The entry criteria are summarized below in the "Diagnosis and Criteria for Inclusion" section. The following three categories of high-risk ACS subjects will be considered for enrollment:

1. **Subjects with NSTE-ACS (unstable angina or NSTEMI) participating in the EARLY-ACS Study (Protocol No. P03684):**

   Clinically stable subjects enrolled in the EARLY-ACS Study under Protocol No. P03684, a double-blind, randomized, parallel-group study of Integrilin (eptifibatide) vs placebo in subjects with high-risk non-ST segment elevation ACS (NSTE-ACS unstable angina or NSTEMI), may be eligible to enroll in the current study after completing the 96-hour primary endpoint of the acute segment of EARLY-ACS treatment (the acute segment of EARLY-ACS treatment is the initial phase of administration of randomized treatment with eptifibatide or matching placebo through catheterization).

2. **Subjects with NSTE-ACS (unstable angina or NSTEMI)enrolling directly into the current study:**

   High-risk NSTE-ACS (unstable angina or NSTEMI) subjects who have been stabilized and are not participating in the EARLY-ACS Study, who qualify in accordance with the entry criteria of the current Protocol No. P04103 may be eligible to enroll in the current study.

3. **Subjects with STEMI:**

The entry criteria are described below in the "Diagnosis and Criteria for Inclusion" section.

Measuring Outcomes: The planned termination of the study will occur after all subjects have been followed for a minimum of 2.5 years and a primary endpoint event has been documented in at least 5250 subjects. If at least 5250 subjects have not met at least one documented primary endpoint event within 2.5 years of the completion of enrollment, the study will continue until this number of events has accumulated. All subjects, including subjects who are discontinued from treatment, will be monitored for any clinical endpoint event until the termination of the study.

A Clinical Events Committee (CEC) will be created to review and adjudicate each suspected clinical endpoint event without unblinding treatment. The suspected clinical endpoint events are listed below and should be reported via the clinical endpoints module on the eCRF:

Death from any cause, MI, unstable angina, all revascularization (including both coronary and non-coronary), stroke, any CV event leading to hospitalization, and CHF.

A Data Safety Monitoring Board (DSMB) will be created to further protect the rights, safety, and well being of subjects who will be participating in this study by monitoring the progress and results. The DSMB will analyze the safety results as well as the overall rate of clinical endpoint events.

An independent LDL-C Monitoring Committee (LMC) will be created to periodically review the achieved LDL-C results and advise the Executive Group within the Operations Committee regarding potentially increasing the target number of primary endpoint events if the difference in median LDL-C between treatment groups is less than anticipated.

Randomized Treatment Assignment: At randomization all subjects entered into this study will receive randomized, double-blind treatment assignment in a 1:1 ratio to either Ezetimibe/Simvastatin Combination 10/40 or simvastatin 40 mg QD. Study drug will be administered once daily in the evening. Initially, all subjects will be assigned to receive randomized treatment comprising three tablets as follows:

- One Ezetimibe/Simvastatin Combination 10/40 tablet (single tablet containing ezetimibe 10 mg and simvastatin 40 mg) and two simvastatin 40 mg placebo tablets; or

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- One Ezetimibe/Simvastatin Combination 10/40 placebo tablet, one simvastatin 40 mg tablet, and one simvastatin 40 mg placebo tablet.

After randomization subjects will be seen at the end of Month 1 and Month 4, and every 4 months, thereafter.

For clarity regarding the changes to drug dosing in this Amendment #5, the following section reviews the current protocol procedure for drug allotment. Treatment is provided in 3 bottles: Bottle A, Bottle B, and Bottle C. Subjects are to take 1 tablet from each bottle once each day in the evening. At the time of treatment assignment, medications in the bottle were as follows:

- ***For subjects assigned to receive Ezetimibe/Simvastatin Combination 10/40: Bottle A contained Ezetimibe/Simvastatin Combination 10/40 tablets. Bottle B and Bottle C each contained matching placebo tablets for Simvastatin 40 mg;***

- ***For subjects assigned to receive simvastatin 40 mg: Bottle A contained matching placebo tablets for Ezetimibe/Simvastatin Combination 10/40 tablets. Bottle B contained simvastatin 40 mg tablets. Bottle C contained matching placebo tablets for Simvastatin 40 mg.***

Monitoring LDL-C and Increasing Simvastatin Dose: ***Earlier in the trial prior to this current Amendment #5, if a subject had 2 consecutive LDL-C measurements >79 mg/dL (>2.0 mmol/L), then that subject was to have his/her simvastatin dose increased to 80 mg in a double-blind manner at the next regularly scheduled visit. To achieve the increase in the simvastatin dose to 80 mg without unblinding treatment, a simvastatin 40 mg tablet replaced a simvastatin 40 mg placebo tablet in the dosing regimen Bottle C. To avoid alerting investigators to subjects receiving a total dose of simvastatin 80 mg QD, "dummy titration" subjects were called at random from across the whole study. The ratio of subjects with LDL-C >79 mg/dL (>2.0 mmol/L) to "dummy titration" subjects was 2:1.***

Thus, subjects who had the dose of simvastatin increased to 80 mg, medications in the bottles were as follows:

- ***For subjects originally assigned to receive Ezetimibe/Simvastatin Combination 10/40, but were to increase the simvastatin component to 80 mg: Bottle A contained Ezetimibe/Simvastatin Combination 10/40 tablets. Bottle B contained matching placebo tablets for simvastatin 40 mg. Bottle C contained simvastatin 40 mg tablets;***

- ***For subjects originally assigned to receive simvastatin 40 mg, but were to increase the simvastatin dose to 80 mg: Bottle A contained matching placebo tablets for Ezetimibe/Simvastatin Combination 10/40 tablets. Bottle B contained simvastatin 40 mg tablets. Bottle C contained Simvastatin 40 mg tablets.***

"Dummy titration" subjects did not have their medication altered.

With this amendment #5, use of simvastatin 80 mg in the study is modified: No additional subjects will have their simvastatin dose increased to 80 mg. Subjects already receiving study medication that includes a simvastatin dose of 80 mg will have their medications reevaluated as described below.

Recent USA labeling changes for simvastatin 80 mg based on findings from large clinical trials and other databases suggest that the risk of serious muscle toxicity with simvastatin 80 mg is greater than that seen with certain newer statins that can produce similar or greater LDL-C lowering. The increased risk is greatest during the first year of treatment. With this amendment #5, no additional subjects will have their simvastatin dose increased to 80 mg. Subjects already receiving simvastatin 80 mg will be managed as follows:

- ***Subjects who have been taking the simvastatin dose of 80 mg for less than 12 months will have their dose decreased to 40 mg. The subjects will be contacted as soon as possible, informed of the changes to the trial, and instructed to stop taking medication from Bottle C;***
- ***Subjects who have been tolerating the simvastatin dose of 80 mg for 12 months or longer without evidence of significant toxicity will continue on the 80 mg dose and do not need to be contacted early unless they are known to be taking amlodipine or ranolazine concomitantly [see below and section 7.6.6]).***

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To minimize the effect of these simvastatin dose changes on the study blind, a proportion of subjects who had already been recalled as a "dummy titration" subject for testing of LDL-C but did not have their simvastatin dose increased to 80 mg will be contacted similarly and instructed to discontinue taking medication from Bottle C. The ratio of subjects who had been actually receiving simvastatin 80 mg for less than 12 months to "dummy titration" subjects who will be contacted will be 2:1.

The process will be managed as follows with assistance from the Sponsor's designee:

- ***Each site will be provided with a list of subjects at that site who need to be contacted;***
- ***The site must contact the subjects on the list and do the following:***
- ***Review the changes to simvastatin dosing and answer all questions related to the trial;***
- ***Instruct the subject to stop taking medication from Bottle C;*** • ***Remind the subject to return for the next scheduled visit for providing informed consent. Collecting informed consent may occur sooner at an unscheduled visit if appropriate and feasible;***
- ***The site must record all changes in the subject's records and register in the IVRS.***

Subjects who are not on the site list for contacting will be managed as follows:

- ***The subject will simply return for the next regularly scheduled visit;***
- ***At the next regularly scheduled visit or sooner if appropriate, the site will review the changes to simvastatin dosing and answer all questions related to the trial. The subject must provide written informed consent to continue in the trial;***
- ***If the subject decides to avoid the possibility of receiving the simvastatin 80 mg dose, the site will instruct the subject to stop taking medication from Bottle C;***
- ***The site must record all changes in the subject's records and register in the IVRS.***

All subjects who stop taking medication from Bottle C will have their LDL-C measured for the trial no later than the next scheduled visit. If deemed medically appropriate by the investigator, subjects who stop Bottle C should return to the clinic earlier for an LDL-C assessment.

Study Drug* Interruption and Discontinuation Due to Elevated LDL-C: *Any subject found to have an LDL-C concentration ≥100 mg/dL (>2.6 mmol/L) at 2 consecutive observations should be discontinued from study medication at the investigator's discretion, but will be monitored for any clinical endpoint event until the termination of the study.

With this amendment #5, subjects who must receive the dihydropyridine amlodipine or the medication ranolazine concomitant with study medication will have their simvastatin dose limited to a maximum of 40 mg, regardless of whether the subjects were tolerating the simvastatin 80 mg dose for 12 months or longer. Subjects receiving amlodipine or ranolazine with study medication that includes simvastatin 80 mg will need to either reduce the simvastatin dose to 40 mg or stop taking the prescribed amlodipine or ranolazine. The potential use of alternative medications to amlodipine or ranolazine must be coordinated with the subjects' physician. The reduction of the simvastatin dose in subjects who are unable to switch to an alternative to amlodipine or ranolazine will be managed as follows:

- ***With assistance from the Sponsor's designee the site must identify subjects receiving a simvastatin dose of 80 mg plus amlodipine or ranolazine as follows:***

- ***Each site will be provided with a list of all subjects at that site who are receiving study medication that includes a simvastatin dose of 80 mg and a dihydropyridine (Note that this list***

will include any dihydropyridine because specific dihydropyridines are not being recorded in the trial database. However, the dosing restriction with amlodipine and simvastatin does <u>not</u> apply to other allowed agents in this class such as nifedipine, felodipine, and nicardipine). The list will also include some dummy titration subjects. The ratio of subjects receiving simvastatin 80 mg to dummy titration subjects will be 2:1. The site will review the local documentation for the subjects on the list and identify those subjects who are actually receiving the dihydropyridine amlodipine;

- ***The site will review the local documentation of all subjects at that site and identify those subjects who are receiving either amlodipine or ranolazine concomitantly to study medication.***

- ***The site must contact each subject identified to be taking either of these medications and inform them of the need either to stop taking amlodipine or ranolazine or to stop taking medication from Bottle C. The option of stopping amlodipine or ranolazine with the possible substitution of alternative medications or modification of other medications must be carefully coordinated with the subject's physician, including appropriate follow-up after a potential change;***

- ***At the next regularly scheduled visit or sooner if appropriate, the site will review the changes to simvastatin dosing and answer all questions related to the trial. The subject must provide written informed consent to continue in the trial;***

- ***The site will reinforce to any subject receiving study medication and concomitant amlodipine or ranolazine of the need to avoid all other prohibited drugs and report promptly any unexplained muscle symptoms, which will trigger laboratory assessment of CPK;***

- ***The site must record all changes in the subject's records and register in the IVRS.***

All subjects who stop taking medication from Bottle C will have their LDL-C measured for the trial no later than the next schedule visit. If deemed medically appropriate by the investigator, subjects who stop Bottle C should return to the clinic earlier for an LDL-C assessment.

***Study Drug* Interruption and Discontinuation Due to Elevated Transaminase Activity:** If a subject is found to have an alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) measurement at least 3 times the upper limit of normal (≥3 x ULN) believed to be related to study drug, then the subject is to return in approximately 1 week to repeat the blood work. If the same transaminase activity is ≥3 x ULN on two consecutive occasions, the study medication will be interrupted. The subject's laboratory tests will be repeated approximately every 2 weeks until the transaminase activity decreases to <2 x ULN, at which time study drug may be restarted at the discretion of the investigator following discussion with the sponsor's clinical monitor. Treatment is to be restarted with the same double-blind treatment as assigned at randomization. A subject who goes on to have a second episode of two consecutive observations of transaminase activity ≥3 x ULN believed to be related to study drug is to be discontinued from study medication, but will be monitored for any clinical endpoint event until the termination of the study.

Note: If the liver function test criterion necessitating study medication discontinuation is met, this constitutes an adverse event of special interest (AESI). AESIs will be analyzed in a special section of the clinical study report (CSR).

Study Drug Interruption and Discontinuation Due to Elevated Creatine Phosphokinase (CPK) Activity: All subjects enrolling in the study will be advised to report promptly any unexplained or unusual muscle symptoms (eg, pain, tenderness, or weakness) to the investigator, which will prompt the measurement of a serum CPK concentration. Serum CPK will be routinely measured at baseline ***and each regularly scheduled visit*** (***see Study Flow Chart)*** in all subjects. ***CPK measurement is included in the routine Abbreviated and Extended Safety Panels performed at specified visits (effective 28 SEP 2010, as described in Memo 217 to Principal Investigators and Research Coordinators).***

At any time during the study, should there be an increase in a subject's CPK level to ≥5 x ULN believed to be related to study drug, the following actions will be implemented according to the situation:

1. CPK ≥10 x ULN with unexplained muscle symptoms consistent with myopathy ***(weakness, pain, soreness not due to new exercise, unusual physical activity, or trauma)***:

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a. Study medication is to be interrupted immediately and CPK is to be measured again as soon as possible.

b. If the repeat CPK measurement and further clinical evaluation confirm the diagnosis or suspicion of myopathy, study medication is NOT to be resumed.

c. Study drug may only be resumed if there is no suspicion that the prior CPK elevation reflected drugrelated myopathy. In such cases, study drug is to be restarted with the same double-blind treatment as assigned at randomization ***with appropriate CPK monitoring***.

2. CPK ≥5 x ULN with no clinical signs of myopathy:

a. The subject is to be instructed to refrain from activities that may have contributed to the elevated CPK and CPK is to be measured again as soon as possible. The subject may continue to receive study medication.

b. If the repeat CPK measurement confirms the observation of elevated CPK levels ***≥5 x ULN***, the subject will have the blood work repeated weekly and may continue to receive study medication, ***provided the suspicion of statin-related myopathy is low. If the CPK level is >10xULN after one to two weeks, however, study medication should be discontinued. The subject should have blood work repeated weekly until the event resolves***.

c. If the CPK value decreases to <2 x ULN, blood work ***may*** be resumed on its regular schedule.

3. CPK ≥5 x ULN and <10 x ULN with unexplained or unusual symptoms consistent with myopathy in the absence of muscle trauma:

a. The subject is to be instructed to refrain from activities that may have contributed to the elevated CPK and CPK is to be measured again as soon as possible. The subject may continue to receive study medication after the first observation of elevated CPK, although the investigator should interrupt treatment, if clinically warranted ***(eg, if symptoms progress or persist or there is otherwise strong suspicion of statin-related myopathy)***.

b. If the repeat CPK measurement confirms the observation of elevated CPK levels and further clinical evaluations confirm the diagnosis or suspicion of myopathy, study medication is to be discontinued immediately. The subject will have the blood work repeated weekly until the event resolves.

Note: ***As stated above, subjects with asymptomatic mild elevations in CPK may continue study drug, but with close monitoring and early, repeat measurement of CPK. However, if the CPK remains elevated (>10xULN regardless of symptoms or ≥5 x ULN and <10 x ULN with persistent unexplained symptoms, renal dysfunction, or liver function abnormalities such as an ALT elevation to >1.5xULN), study drug should be stopped.*** If a subject is reported as having myopathy, rhabdomyolysis, or if the CPK criterion necessitating study medication discontinuation is met, this constitutes an AESI. AESIs will be recorded in the database, monitored by the DSMB, and evaluated and reported in the clinical study report.

Myopathy is defined by either of the following criteria:

1. Otherwise unexplained muscle pain, weakness, or tenderness with CPK ≥10 x ULN; or
2. Otherwise unexplained muscle pain, weakness, or tenderness with two consecutive observations of CPK ≥5 x ULN and <10 x ULN.

At any time during the study, if a subject should present with symptoms consistent with rhabdomyolysis, study medication is to be discontinued immediately.

Rhabdomyolysis is defined by either of the following criteria:

1. Otherwise unexplained muscle pain, weakness, or tenderness and CPK ≥10,000 mU/mL; or
2. Otherwise unexplained muscle pain, weakness, or tenderness with CPK ≥10 x ULN with evidence of renal injury.

Renal injury is defined by at least one of the following three criteria:

1. Increased creatinine levels (absolute increase of ≥0.5 mg/dL or a relative increase of ≥50% compared with the last available creatinine level preceding the event); 2. Myoglobinuria; or

3. Brown urine.

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Type of Blinding: Double-blind Ezetimibe/Simvastatin Combination 10/40 or simvastatin 40 mg.

Sample Size (Including Ratio of Subjects Assigned to Treatments)/Power: ***Approximately*** 18,000 subjects will receive randomized treatment assignment to either Ezetimibe/Simvastatin Combination 10/40 or simvastatin 40 mg QD, with up to 9000 subjects per treatment group. Treatment with Ezetimibe/Simvastatin Combination 10/40 is expected to result in an approximate mean absolute reduction of 15 mg/dL (0.39 mmol/L) in LDL-C concentration compared with treatment with simvastatin 40 mg, and this is hypothesized to result in an approximate 9.375% reduction in hazard in the primary endpoint event (incidence of CV death, major coronary events, or non-fatal stroke) at 2 years for Ezetimibe/Simvastatin Combination 10/40 over simvastatin 40 mg.

The sample size will be ***approximately*** 18,000 subjects with the trial continuing until accrual of approximately 5250 primary endpoint events, which will provide power in the range of 90%. This sample size is determined from a statistical model approach based on pooled blinded endpoint rates and evaluates the effects of a reduced treatment effect in the first 6 months, enrollment rate, follow-up duration, lag in event rate reporting, differences in population event rates (STEMI and NSTE) and drop-out on power and total event accumulation during the trial. The goal of sample size modeling is to maintain trial power at approximately 90% while minimizing total trial duration. The final sample size will be determined by the statistical modeling approach when adequate patient experience has been accumulated to result in a stable estimate of the primary endpoint event rate. Full details of the modeling approach will be provided in a separate sample size statistical plan.

Following it's periodic reviews, the independent LMC may advise the Executive Group within the Operations Committee regarding the targeted number of primary endpoint events if the difference in median LDL-C between treatment groups is less than anticipated.

Subject Replacement Strategy: No subject will be replaced.

Randomization: Centralized.

Stratification: Randomized treatment assignment will be stratified by three factors:

- Randomized treatment assignment for subjects entering the current study (P04103) from the EARLY-ACS study (P03684): assigned eptifibatide or placebo;
- Experience with lipid-lowering therapy (**Appendix 4**): subjects receiving chronic prescription lipid-lowering therapy for >4 weeks prior to and continuing until admittance into a hospital or subjects not receiving chronic prescription lipid-lowering therapy. Enrollment of subjects receiving chronic prescription lipid-lowering therapy will be limited to 50% of all subjects within each country;
- High-risk ACS diagnosis: NSTE-ACS (unstable angina or NSTEMI) or STEMI.

Diagnosis and Criteria for Inclusion: The high-risk ACS population will comprise both subjects with NSTEACS (unstable angina or NSTEMI) with or without MI and subjects with STEMI according to the following conditions:

1. A subject with NSTE-ACS according to the following criteria may be enrolled:

   a. A NSTE-ACS (unstable angina or NSTEMI) subject participating in the EARLY-ACS Study (Protocol No. P03684) who has been clinically stabilized will be eligible for entry in the current study under Protocol No. P04103 □10 days (□240 hours) of presenting to the hospital. The subject must complete the acute segment of EARLY-ACS treatment (the acute segment of EARLY-ACS treatment is the initial phase of administration of randomized treatment with eptifibatide or matching placebo through catheterization) and be clinically stable before enrolling in the current study.

-OR-

   b. A subject not participating in the EARLY-ACS Study, but who is defined as NSTE-ACS (unstable angina or NSTEMI) by meeting all of the following criteria, and has been clinically stable for at least 24 hours prior to screening/randomization will be eligible to enter directly into the current study □10 days (□240 hours) of acute admittance into a hospital:

      (1) The subject has experienced symptoms of cardiac ischemia at rest prompting acute care hospitalization with at least one episode lasting at least 10 minutes.

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(2) ≥50 years of age; and

(3) ANY 1 of the following criteria:

(a) Electrocardiogram changes by either of the following:

[1] New or presumably new ST-segment depression ≥0.1 mV in at least 2 contiguous ECG leads; or

[2] Transient (<30 minutes) ST-segment elevation ≥0.1 mV in at least 2 contiguous ECG leads.

(b) Any of the following cardiovascular biomarkers elevated > ULN:

[1] Troponin I;

[2] Troponin T; and/or

[3] Creatine kinase-MB fraction (CK-MB).

(c) Diabetes mellitus;

(d) History of prior MI;

(e) History of peripheral arterial disease;

(f) History of cerebrovascular disease;

(g) History of CABG ≥3 years prior to entry (Note: This is 1 item in a list of 8 criteria. If the subject has had CABG within the 3 years prior, they still may be eligible if at least one criterion of a–f or h from this list are met.);

(h) Multivessel coronary artery disease previously documented by catheterization (2 or 3 vessels with ≥50% stenosis) including the catheterization performed during the index admission for the qualifying event.

Note: It is strongly recommended that each high-risk NSTE-ACS (unstable angina or NSTEMI) subject not enrolled in the EARLY-ACS study undergo a cardiac catheterization within 72 hours of acute presentation. All study sites must have access to catheterization or other invasive procedures to ensure that all subjects are provided a similar standard of care.

Key Inclusion Criteria:

Note: A subject is considered to be receiving chronic prescription lipid-lowering therapy if he/she has been receiving any prescription lipid-lowering therapy continuously for >4 weeks prior to and continuing until the qualifying ACS hospital admission. All other subjects (including those who initiate prescription lipid-lowering therapy after the qualifying ACS hospital admission) are considered to be" lipid-therapy naïve."

1. Subject must meet the following criteria for LDL-C concentrations at the time of admittance into a hospital (Each measurement of LDL-C performed within the first 24 hours of admittance must meet the criteria):

a. A lipid-therapy naïve subject will be eligible to enroll if his/her LDL-C concentration is ≥50 mg/dL (≥1.3 mmol/L) and ≥125 mg/dL (≥3.2 mmol/L);

b. A subject receiving chronic prescription lipid-lowering therapy will be eligible to enroll, if his/her LDL-C concentration is ≥50 mg/dL (≥1.3 mmol/L) and ≥100 mg/dL (≥2.6 mmol/L).

Note: Observe the following conditions concerning LDL-C concentrations:

(1) Blood lipid levels, including LDL-C, should be measured as close as possible to each subject's presentation to a hospital, but no later than 24 hours after admission. A subject's baseline LDL-C and lipid-lowering-therapy status are to be based on the subject's status at the time of the initial acute event leading to admittance into a hospital.

(2) The specimens do not need to be obtained after fasting. In addition if the blood lipid levels are not measured at the time of admittance, they may be determined later on blood from the subject that was obtained at the time of admittance into the hospital.

(3) If a recent lipid panel (<6 months prior to presentation) is available, the values may be used for subject screening and determination of eligibility if the subject's therapy had not changed since the lipid measurement and if no specimen was drawn within the first 24 hours after admission to a hospital.

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(4) If only a total cholesterol (TC) level is available at the time of admission, the subject will still be eligible if TC concentrations meet the following criteria at the time of admission and repeat preferably fasting lipid measurements obtained as soon as possible (preferably within 24 hours of admission) meet the above LDL-C criteria:

(a) TC concentration ≥190 mg/dL (≥4.9 mmol/L) for a lipid-therapy naïve subject;

(b) TC concentration ≥150 mg/dL (≥3.9 mmol/L) for a subject receiving chronic prescription lipidlowering therapy.

2. Subject must have a plasma triglyceride (TG) level ≥350 mg/dL (≥4.0 mmol/L). Subjects found to have a non-fasting TG >350 mg/dL (>4.0 mmol/L) upon admittance into a hospital, but have TG <1500 mg/dL (<17.0 mmol/L), must have TG ≥350 mg/dL (≥4.0 mmol/L) on a fasting specimen obtained as soon as possible (preferably within 24 hours of admission).

3. A subject in whom a PCI is planned as management for the qualifying ACS event should undergo PCI prior to Randomization and within the 10-day period after initial hospitalization for the qualifying ACS event. Although subsequent staged PCI procedures are permitted, all planned PCIs that are known at the time of screening must be completed within 30 days of Randomization. Whenever possible, PCI procedures (including staged procedures) known to be indicated at the time of screening should be completed prior to Randomization.

Key Exclusion Criteria: A subject will be excluded from entry if any of the criteria listed below are met:

1. Subject who is clinically unstable. A subject is considered clinically unstable if he/she displays any of the following events within 24 hours prior to Screening/Randomization: a. Hemodynamic events:
   (1) Hypotension, defined as sustained systolic blood pressure of <90 mmHg due to cardiac failure with associated symptoms;
   (2) Unstable or severe Pulmonary edema/decompensated CHF;
   (3) Acute mitral regurgitation;
   (4) Acute ventricular septal defect.
   b. Recurrent symptoms of cardiac ischemia:
   c. Stroke or transient ischemic attack (TIA);
   d. Arrhythmic events:
   (1) Ventricular fibrillation;
   (2) Sustained ventricular tachycardia lasting >30 seconds or in association with symptoms; (3) Complete heart block;
   (4) High grade second degree heart block.
2. Subject who plans or undergoes CABG in response to the initial episode of ACS.
3. Subject requires the following concomitant medications: cyclosporine, diltiazem, danazol, amiodarone, verapamil, niacin, fibrates as concomitant medications or any of the potent CYP3A4 inhibitors, itraconazole, ketoconazole, erythromycin, clarithromycin, and telithromycin, HIV protease inhibitors, nefazodone, probucol, resins, grapefruit juice >1 quart/day, torceptrapib, and any investigational drugs. Routes of administration other than oral or parenteral (eg, topical, intraocular, otic) of antifungal or antibiotics are acceptable. Shortterm therapy of any prohibited medication is acceptable, provided study medication is interrupted during the administration and restarted after short-term therapy is completed.
4. Subject is a pregnant or lactating woman, or woman intending to become pregnant.
5. Subject has active liver disease or persistent unexplained serum transaminase elevations (□2 x ULN). Subject with a transient increases in serum transaminases due to the index MI may be enrolled.
6. Subject has calculated creatinine clearance (CrCl) <30 mL/min or dialysis within 30 days. Creatinine clearance is to be calculated according to the Cockcroft-Gault equation.
7. Subject has a history of alcohol and/or drug abuse.
8. Subject has an allergy/sensitivity to any statin, ezetimibe, and/or their excipients.

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9. The investigator feels that discontinuation of existing lipid-lowering regimen poses a risk to the subject.
10. Subject is receiving chronic prescription lipid-lowering therapy with LDL-C lowering potency greater than simvastatin 40 mg (**Appendix 4**).
    a. Chronic lipid-lowering therapy with LDL-C potency greater than simvastatin 40 mg are:
        (1) All doses of simvastatin >40 mg;
        (2) All doses of atorvastatin 40 mg;
        (3) All doses of rosuvastatin;
        (4) All doses of Ezetimibe/Simvastatin Combination;
        (5) Ezetimibe coadministered with any dose of any statin.
    b. For the purposes of this protocol, all other chronic prescription lipid lowering therapies will be considered equal or less potent than simvastatin 40 mg QD and subjects taking such therapies may be considered for enrollment.
11. Subject with prior enrollment in this current study under Protocol No. P04103.

Test Product, Dose, Mode of Administration: Double-blind Ezetimibe/Simvastatin Combination 10/40 tablets PO QD in the evening. Ezetimibe/Simvastatin Combination is identified as SCH 465981.

Reference Therapy, Dose, Mode of Administration:

Simvastatin 40 mg tablets PO QD in the evening (double-blind).

Placebo (double-blind).

Ezetimibe/Simvastatin Combination -matching placebo tablets will be identical in image to the Ezetimibe/Simvastatin Combination 10/40 tablets.

Simvastatin placebo tablets will be identical in image to the simvastatin 40 mg tablets.

Duration of Treatment: Duration of treatment is anticipated to be a minimum 2.5 years.

Criteria for Evaluation: See **Synopsis Table 1** for a description of composite endpoint organization.

1. Primary Efficacy Endpoint Measure:

The primary efficacy endpoint measure will be the time from randomization until the first occurrence of one of the following: CV death, major coronary events (non-fatal MI, documented unstable angina that requires admission into a hospital, all coronary revascularization with either PCI or CABG occurring at least 30 days after randomization), or non-fatal stroke.

2. Secondary Efficacy Endpoint Measures:

a. Time from randomization until the first occurrence of death due to any cause, major coronary events, or non-fatal stroke.

b. Time from randomization until the first occurrence of CHD death, non-fatal MI, or urgent coronary revascularization with either PCI or CABG occurring at least 30 days after randomization

c. Time from randomization until the first occurrence of CV death, non-fatal MI, documented unstable angina that requires admission into a hospital, all revascularization (including both coronary and non-coronary) occurring at least 30 days after randomization, and non-fatal stroke.

3. Tertiary Efficacy Endpoint Measures:

a. **Individual Endpoint Measures:**

The individual tertiary outcomes measures will be the time from randomization until the first occurrence for each of the following individual events: death from any cause, CHD death, CV death, MI, documented unstable angina that requires admission into a hospital, all coronary revascularization with either PCI or CABG occurring at least 30 days after randomization, urgent coronary revascularization with either PCI or CABG occurring at least 30 days after randomization, all revascularization (including both coronary and non-coronary) occurring at least 30 days after randomization, stroke, any cardiovascular event leading to admission into a hospital, CHF that requires hospitalization occurring at least 30 days after randomization.

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b. Reductions in LDL-C and hs-CRP:

The LDL-C/hs-CRP outcomes measure will be the percentage of subjects achieving concentrations of LDL-C <70 mg/dL (<1.8 mmol/L) in addition to hs-CRP <2.0 mg/L following 1 month and 4 months of treatment with Ezetimibe/Simvastatin Combination or simvastatin.

4. Safety Measurements:

Clinical evaluations will include the evaluation of routine adverse events, vital signs and relevant laboratory measurements. Events of special interest that will be evaluated will include consecutive elevations of AST and/or ALT to □3 x ULN, incidence of myopathy, incidence of cholecystectomies, and incidence of all gallbladder-related adverse events.

Synopsis Table 1 Efficacy Endpoints

Primary Endpoint Events and Primary Composite Endpoint	Secondary Composite Endpoint (a)	Secondary Composite Endpoint (b)	Secondary Composite Endpoint (c)	Tertiary Individual Endpoints
CV Death, Major Coronary Events, and Stroke	All Death, Major Coronary Events, and Stroke	CHD Death, Non-fatal MI, and Urgent Coronary Revascularization	CV Death, Vascular Events, and Stroke	All Individual Endpoints[a]
CV Death			CV death	CV death
	Death from any cause			Death from any cause
		CHD death		CHD death
Non-fatal MI[b]	Non-fatal MI[b]	Non-fatal MI[b]	Non-fatal MI[b]	
				MI[b]
Documented unstable angina requiring hospitalization	Documented unstable angina requiring hospitalization		Documented unstable angina requiring hospitalization	Documented unstable angina requiring hospitalization
All coronary revascularization with PCI or CABG[c]	All coronary revascularization with PCI or CABG[c]			All coronary revascularization with PCI or CABG[c]
		Urgent coronary revascularization with PCI or CABG[c]		Urgent coronary revascularization with PCI or CABG[c]

			All revascularization[c,d]	All revascularization[c,d]
Non-fatal Stroke[b]	Non-fatal Stroke[b]		Non-fatal Stroke[b]	
				Stroke[b]
				Any CV event leading to hospitalization
				CHF that requires hospitalization[e]
				Dual Goal for LDL-C/hs-CRP[f]

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CABG = Coronary Artery Bypass Grafting; CHD = Coronary Heart Disease; CHF = Congestive Heart Failure; CV = Cardiovascular; MI = Myocardial Infarction; PCI = Percutaneous Coronary Intervention

a All individual endpoints are to be analyzed as a tertiary objective.

b All MIs and all strokes are to be analyzed individually. However, because each composite endpoint already captures deaths caused by MI or stroke, only non-fatal MIs and non-fatal strokes are components of the composite endpoints.

c Revascularization must occur at least 30 days after randomization to be included as a clinical endpoint event in the analyses.

d All revascularization includes coronary revascularization and non-coronary revascularization.

e CHF that requires hospitalization must occur at least 30 days after randomization to be considered a clinical endpoint event.

f Percentage of subjects achieving concentrations of LDL-C <70 mg/dL (<1.8 mmol/L) in addition to hs-CRP <2.0 mg/L following 1 month and 4 months of treatment with Ezetimibe/Simvastatin Combination or simvastatin.

Statistical Methods: The statistical methods described here are intended for the analyses of the primary and secondary hypotheses only.

The primary efficacy outcome measure will be the time from randomization until the first occurrence of one of the following: CV death, major coronary events (non-fatal MI, documented unstable angina that requires admission into a hospital, all coronary revascularization with either PCI or CABG occurring at least 30 days after randomization), or non-fatal stroke. The primary hypothesis is that in stabilized high-risk ACS subjects, the administration of Ezetimibe/Simvastatin Combination compared with simvastatin will reduce the incidence of the composite endpoint of CV death, major coronary events, and non-fatal stroke. This hypothesis will be evaluated using a Cox proportional-hazard model with covariates of treatment and stratification factors (early use of eptifibatide, chronic prescription lipid-lowering therapy experience, and high-risk ACS diagnosis). Estimates of the hazard ratios and associated 95 percent confidence intervals comparing simvastatin with Ezetimibe/Simvastatin Combination will be provided with the use of this model. The primary statistical analysis will include all subjects who receive randomized treatment assignment. The secondary hypotheses will be evaluated using similar methodology.

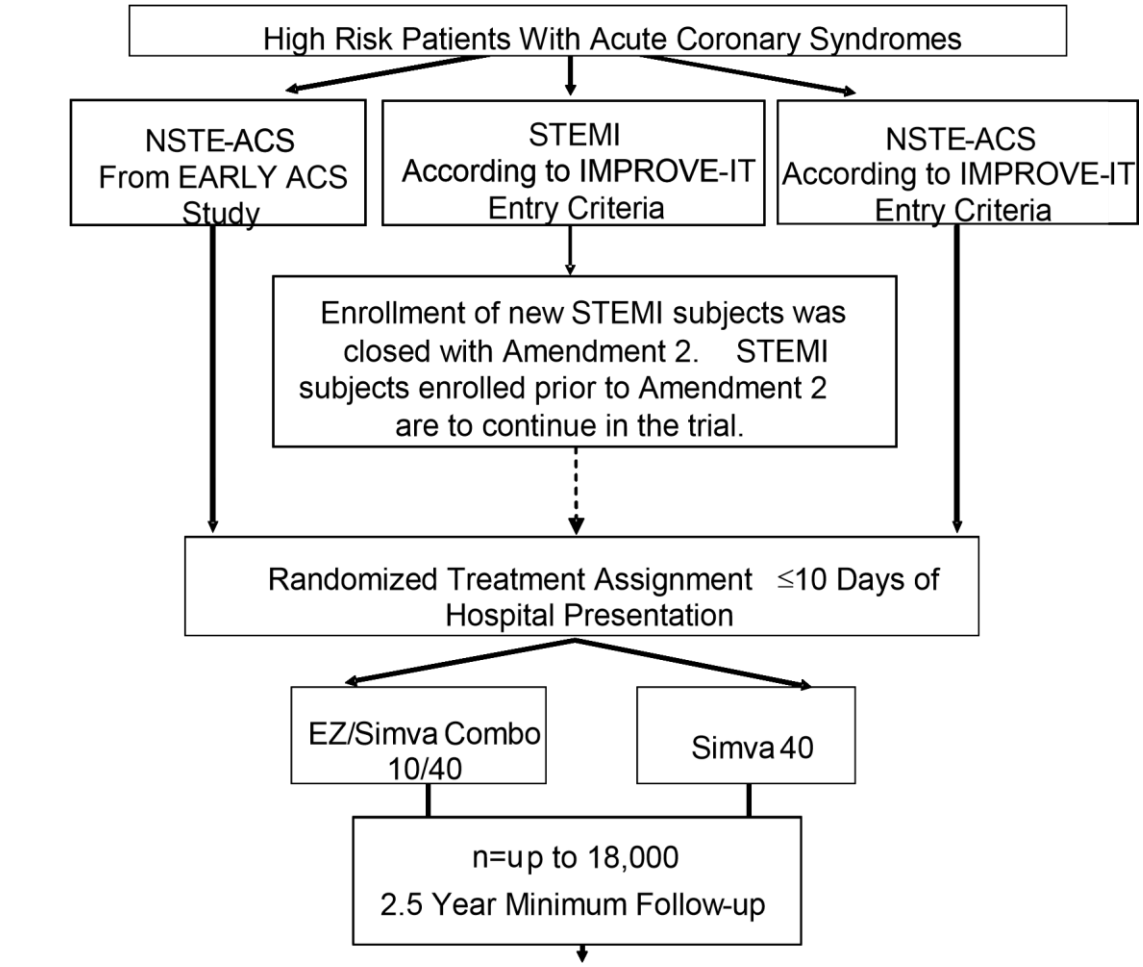
Because revascularizations occurring up to 30 days after randomization will not be included in the pre-specified endpoints, the effect of these events will be assessed by sensitivity analyses on the primary endpoints.

Two interim efficacy ***analyses*** will be performed when approximately 50% ***and 75%*** of the expected total primary events are available. The primary analysis will be based on the adjudicated events. Supportive analyses will be performed on both adjudicated and un-adjudicated events. The O'Brien-Fleming methodology will be implemented to protect the overall type I error of 0.05 using the software East 3. Specifically, it is expected that a nominal alpha level of 0.003 will be used for the ***first*** interim analysis ***(50% of events) and a nominal alpha level of 0.0184 will be used for the second interim analysis (75% of events). Overwhelming efficacy for early study termination minimally requires significance for the primary efficacy endpoint at the specified nominal significance levels and a directionally consistent reduction in total mortality.*** For the final analysis, the primary endpoint will be tested at an expected nominal alpha level of 0.04***38***. Details for the interim analyses will be provided in the DSMB charter.

As described above, the LMC will periodically review the achieved LDL-C results and advise the Executive Group within the Operations Committee regarding potentially increasing the targeted number of primary endpoint events if the difference in median LDL-C between treatment groups is less than anticipated. The LMC review procedure will ensure that the number of primary efficacy endpoints is adequate to answer the main trial question. Details for the LMC operations and analyses are provided in the LMC charter.

Descriptive statistics will be provided for safety data. All the safety and efficacy data will include all subjects who receive randomized treatment assignment.

2.1 Study Design Diagram



Primary Endpoint: CV Death, Nonfatal MI, Hospital Admission forr Unstable Angina, Revascularization >30 Days, Nonfatal Stroke

2.2 Study Flow Chart

	Treatment Assignment	Participation With Assigned Treatment							Early Discon of Assigned Treatment	
	Screening/ Ran[a]	Month 1[b] Visit	Month 4,8 Visits[b]	Month 12 Visit[b]	Month 16 Visit[b]	Later 4 Month Visits	Annual Visits Only[b]	Final Visit	At Early Discon[c]	Continuing Thru End of Trial[c]
Informed Consent and Medical History	X									
Review Inclusion/Exclusion Criteria	X									
CV Concomitant Medications Review	X	X	X	X	X	X	X	X	X	X
Directed Physical Exam & waist circumference	X			X			X	X	X	
Clinic Assessment (BP, Pulse, Weight)	X	X	X	X	X	X	X	X	X	
Central Laboratory Panels:										
Abbreviated Lipid Panel[d]		X	X		X					
Extended Lipid Panel[d]	X[e]			X			X	X	X	
Abbreviated Safety Panel[d,f]		X	X		X					
Extended Safety Panel[d,f]	X			X			X	X	X	
Calculated Creatinine Clearance	X									
Pregnancy Test[g]	X	X	X	X	X	X	X	X	X	
Blood Sample: DNA Extraction & Storage[h]	X									

hs-CRP[i]	X	X	X[i]	X			X	X		
Cardiovascular Biomarker Analyses[i,j]	X	X	X[i]	X			X	X		
Quality of Life Assessment	X	X	X	X	X	X	X	X	X	
Pharmacoeconomic Assessment		X	X	X	X	X	X	X	X	
Primary Clinical Endpoint Event		X	X	X	X	X	X	X	X	X
Adverse Event Evaluation		X	X	X	X	X	X	X	X	
Adverse Events of Special Interest (AESI)		X	X	X	X	X	X	X	X	X
Dispense Drug	X		X	X	X	X	X			
	Treatment Assignment	Participation With Assigned Treatment							Early Discon of Assigned Treatment	
	Screening/ Ran[a]	Month 1[b] Visit	Month 4,8 Visits[b]	Month 12 Visit[b]	Month 16 Visit[b]	Later 4 Month Visits	Annual Visits Only[b]	Final Visit	At Early Discon[c]	Continuing Thru End of Trial[c]
Collect/Count Unused Medication			X	X	X	X	X	X	X	
Schedule Next Visit	X	X	X	X	X	X	X			

Footnotes and Further Instructions for Study Flow Chart:

[a] Screening/Randomization Visit: Randomized treatment assignment may occur after clinical stabilization in the hospital and after the 96-hour primary endpoint of the EARLY-ACS study's acute segment for subjects entering from that study, but □10 days (□240 hours) of acute admittance into a hospital.

[b] Every effort must be made to have subjects appear at the scheduled visit, but the visit schedules must accommodate the availability of subjects and study sites. The recommended visit windows are: Month 1 Visit allow □7 days; Month 4 Visit and subsequent visits allow □14 days.

[c]

After early discontinuation of treatment, subjects will be followed to record AEs (including SAEs) that start 30 days or fewer following the end study medication. Subjects who discontinue study medication early will be followed beyond 30 days to the conclusion of the whole trial via telephone contact according to the specified visit schedule. Subjects will be followed for the occurrence of primary clinical endpoint events, administration of any lipid-lowering treatments, and occurrences of Adverse Events of Special Interest (AESI) which are defined in **Section 7.7.2.2.11** and include (1) defined increases in AST and/or ALT; (2) defined increases in CPK; (3) All AEs reflective of gallbladder-disease; (4) All cholecystectomies; and (5) All occurrences of myopathy and rhabdomyolysis.

d

Abbreviated Lipid Panel, Extended Lipid Panel, Abbreviated Safety Panel, and Extended Safety Panel are defined in **Section 7.6.2** and **Appendix 2**.

e

The initial LDL-C and other lipids drawn in a preferred but not obligate fasting state is to occur as soon as possible after the initial event leading to admittance into a hospital.

f

CPK measurement is included in the routine Abbreviated and Extended Safety Panels (effective 28 SEP 2010, as described in Memo 217 to Principal Investigators and Research Coordinators). See Section 7.6.4.2. All subjects enrolling in the study will be advised to report promptly any unexplained or unusual muscle symptoms (eg, pain, tenderness, or weakness) to the investigator, which will prompt the measurement of a CPK concentration.

g

The local laboratory will perform serum or urine pregnancy test on female subjects of child-bearing potential to determine eligibility at the Screening/Randomization Visit. The central laboratory will perform the serum pregnancy test at each visit through the Month 16 visit. A urine pregnancy test will be performed at each subsequent visit through the end of participation. All female subjects of childbearing potential must have the scheduled pregnancy tests. All women subjects will be instructed to report suspected pregnancies immediately.

h

Blood sample for DNA extraction and storage will be collected only for subjects who have given a separate written informed consent and if the health authorities, ethics committee, and study center agree. Consent and the blood sample for DNA extraction may be collected at any visit.

i hs-CRP and biomarkers are not to be measured at Early Discontinuation of Study Treatment nor at the time of a suspected clinical endpoint event.

j

Up to 10 mL of plasma and 10 mL of serum will be obtained for evaluation of cardiovascular markers of risk, such as markers of inflammation immune activation (eg, neopterin), endothelial function (eg, E-selectin), coagulation (eg, tissue factor), platelet activation (eg, CD40-ligand), hemodynamic perturbation (eg, brain natriuretic peptide [BNP]), metabolic abnormality (eg, Adiponectin), and cholesterol absorption and synthesis (eg, phytosterols and lathosterol). The 10 mL sample of plasma will be divided into three aliquots of equal volume; the first aliquot is to be distributed to Duke Clinical Research Institute (DCRI), the second aliquot to TIMI, and the third aliquot to the Sponsor. Similarly, the 10 mL sample of serum will be divided into three aliquots of equal volume; the first aliquot is to be distributed to Duke Clinical Research Institute (DCRI), the second aliquot to TIMI, and the third aliquot to the Sponsor.

3.0 TABLE OF CONTENTS

3.1 List of Tables

3.2 List of Appendices

4.0 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Table 1 Glossary of Abbreviations and Terms

Protocol No. P04103

4S	Scandinavian Simvastatin Survival Study
ACS	Acute Coronary Syndrome
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Aminotransferase (SGPT)
AST	Aspartate Aminotransferase (SGOT)
ATP	Adult Treatment Panel
BNP	Brain Natriuretic Peptide
BUN	Blood Urea Nitrogen
CABG	Coronary Artery Bypass Grafting
CCU	Cardiac Care Unit
CD	Compact Disk
CEC	Clinical Events Committee
CHD	Coronary Heart Disease
CHF	Congestive Heart Failure
CK-MB	Creatine Kinase MB Fraction
Clinical Endpoint Event	The occurrence of any of the following: death from any cause, CHD death, CV death, MI, documented unstable angina that requires admission into a hospital, all coronary revascularization with either PCI or CABG occurring at least 30 days after randomization, urgent coronary revascularization with either PCI or CABG occurring at least 30 days after randomization, all revascularization (including both coronary and non-coronary) occurring at least 30 days after randomization, stroke, any cardiovascular event leading to admission into a hospital, and congestive heart failure (CHF) that requires hospitalization occurring at least 30 days after randomization.
CFR	Code of Federal Regulations
chronic prescription lipidlowering therapy	Treatment with any prescription lipid-lowering therapy continuously for >4 weeks prior to and continuing until the qualifying ACS hospital admission.
CPK	Creatine Phosphokinase Activity
CrCl	Creatinine Clearance
CRF	Case Report Form
CSR	Clinical Study Report
CTC	Clinical Trial Coordinator

CTD	Clinical Trial Directive
CTT	Cholesterol Treatment Trialists'
CV	Cardiovascular
DAP	Data Analysis Plan
DCRI	Duke Clinical Research Institute

Table 1 Glossary of Abbreviations and Terms

DSMB	Data Safety Monitoring Board
DSS	Drug Safety Surveillance; the Schering Corporation department responsible for the receipt, regulatory assessment, and, in the USA, reporting to FDA of all postmarketing adverse events and all SAEs from clinical trials
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EMEA	European Medicines Agency
EU	European Union
EudraCT number	EudraCT is a database of all interventional clinical trials of medicinal products in the European Community; it has been established in accordance with Directive 2001/20/EC. The database itself is confidential and accessible only to the Competent Authorities of the Member States, the EMEA and the Commission. To provide a unique reference for clinical trials with at least one site in the Community, each trial will be given a unique number - the EudraCT Number, which must be included on all clinical trial applications within the Community and as needed on other documents relating to the trials.
FDA	Food and Drug Administration, USA
Form 1727	The Schering Corporation collection form used to report SAEs to DSS. SAE information can also be provided using a suitable alternative as long as it contains the equivalent information
GCP	Good Clinical Practice
hCG	human Chorionic Gonadotropin
HPS	Heart Protection Study
hs-CRP	high-sensitivity C-Reactive Protein
IATA	International Air Transport Association
IB	Investigator's Brochure
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICU	Intensive Care Unit

IEC	Independent Ethics Committee
IMPQC	Investigational Medicinal Product Quality Complaint
IND	Investigational New Drug Application; legal instrument in the USA that allows study of unapproved, investigational new drugs in human subjects
IRB	Institutional Review Board
ITT	Intent-to-Treat
IUD	Intrauterine Device
IVRS	Interactive Voice Response System
LBBB	Left Bundle Branch Block
LDL-C	Low-Density-Lipoprotein Cholesterol

Table 1 Glossary of Abbreviations and Terms

Protocol No. P04103

LDH	Lactate Dehydrogenase
LMC	LDL-C Monitoring Committee
Major Coronary Events	non-fatal MI, documented unstable angina that requires admission into a hospital, and all coronary revascularization with either percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) occurring at least 30 days after randomized treatment assignment
MI	Myocardial Infarction
MRFIT	Multiple Risk Factor Intervention Trial
NA, N/A	Not applicable
NCEP	National Cholesterol Education Program
NSTE	Non-ST Segment Elevation
PCI	Percutaneous Coronary Intervention
PDF	Portable Document Format
Primary endpoint event	Composite endpoint CV death, major coronary events, and non-fatal stroke
PROVE-IT	Pravastatin or Atorvastatin Evaluation and Infection Therapy Trial
QALY	Quality Adjusted Life Years
RBC	Red Blood Cell
SAE	Serious Adverse Event
SGOT	Serum Glutamic Oxaloacetic Transaminase (AST)
SGPT	Serum Glutamic Pyruvic Transaminase (ALT)
SOP	Standard Operating Procedure
SPRI	Schering-Plough Research Institute, a division of Schering Corporation

STEMI	ST-Elevation Myocardial Infarction
Suspected Clinical Endpoint Event	The occurrence of any of the following: Death from any cause, MI, unstable angina, all revascularization (including both coronary and non-coronary), stroke, any CV event leading to hospitalization, and CHF
TAAL	Test Article Accountability Ledger
TC	Total Cholesterol
TG	Triglycerides
TIA	Transient Ischemic Attack
TIMI	Thrombolysis In Myocardial Infarction
TASIR	Test Article Summary Inventory Record
TNT	Treating to New Targets
ULN	Upper Limit of Normal
USA	United States of America
User ID	User Identification
WBC	White Blood Cell
WHO-ART	World Health Organization Adverse Reaction Terminology

5.0 INTRODUCTION

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6.0 STUDY OBJECTIVES

6.1 Objectives

6.1.1 Primary Objective: To Evaluate the Clinical Benefit of Treatment on Cardiovascular (CV) Death, Major Coronary Events, and Stroke

The primary objective of this study is to evaluate the clinical benefit of Ezetimibe/Simvastatin Combination compared with simvastatin in stabilized ACS subjects – either acute MI or unstable angina. Clinical benefit will be defined as the reduction in the risk of the occurrence of the composite endpoint of CV death, major coronary events, and non-fatal stroke. CV death, major coronary events, and nonfatal stroke are designated primary endpoint events. Major coronary events include non-fatal MI, documented unstable angina that requires admission into a hospital, and all coronary revascularization with either percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) occurring at least 30 days after randomized treatment assignment. Only revascularization events that occur after the first 30 days of treatment will be considered as clinical endpoint events, in order to focus on revascularization events that can be reasonably expected to be affected by treatment and are unrelated to the initial ACS event.

Clinical endpoint events will be defined more specifically by the Clinical Events Committee (CEC) Charter (**Section 9.3.2**).

6.1.2 Secondary Objective: To Evaluate Supportive Composite Endpoints

The secondary objectives of this study are as follows:

1. To evaluate the clinical benefit of Ezetimibe/Simvastatin Combination compared with simvastatin in stabilized ACS subjects on the occurrence of the composite endpoint of death due to all causes, major coronary events, and non-fatal stroke.
2. To evaluate the clinical benefit of Ezetimibe/Simvastatin Combination compared with simvastatin in stabilized ACS subjects on the occurrence of the composite endpoint of death due to coronary heart disease (CHD) (CHD death), non-fatal MI, and urgent coronary revascularization with either PCI or CABG occurring at least 30 days after randomization.
3. To evaluate the clinical benefit of Ezetimibe/Simvastatin Combination compared with simvastatin in stabilized ACS subjects on the composite endpoint of CV death, non-fatal MI, documented unstable angina that requires admission into a hospital, all revascularization ("All revascularization" includes coronary revascularization and non-coronary revascularization) occurring at least 30 days after randomization, and non-fatal stroke.

6.1.3 Tertiary Objectives

The tertiary objectives of this study are as follows:

1. To evaluate the clinical benefit of treatment on individual endpoint events:

   To evaluate the clinical benefit of Ezetimibe/Simvastatin Combination compared with simvastatin in stabilized ACS subjects on each of the following endpoints analyzed individually: death from any cause, CHD death, CV death, MI, documented unstable angina that requires admission into a hospital, all coronary revascularization with either PCI or CABG occurring at least 30 days after randomization, urgent coronary revascularization with either PCI or CABG occurring at least 30 days after randomization, all revascularization (including both coronary and non-coronary) occurring at least 30 days after randomization, stroke, any cardiovascular event leading to admission into a hospital, and congestive heart failure (CHF) that requires hospitalization occurring at least 30 days after randomization.
2. To evaluate the proportion of subjects achieving reductions in LDL-C and hs-CRP:
   a. To evaluate the percentage of subjects achieving endpoint concentrations of LDL-C of <70 mg/dL (<1.8 mmol/L) and hs-CRP of <2.0 mg/L following 1 month and 4 months of treatment with Ezetimibe/Simvastatin Combination compared with simvastatin.
   b. To evaluate the potential relationship between the risk of occurrence of any primary endpoint event and the concentrations of LDL-C and high sensitivityC-reactive protein (hs-CRP) following 1 month and 4 months of treatment with Ezetimibe/Simvastatin Combination or simvastatin.

3. To evaluate safety measurements:

   To evaluate the safety and tolerability of Ezetimibe/Simvastatin Combination compared with simvastatin.

6.2 Hypotheses

6.2.1 Primary Hypothesis: To Evaluate the Clinical Benefit of Treatment on CV Death, Major Coronary Events, and Stroke

In stabilized high-risk ACS subjects, the administration of Ezetimibe/Simvastatin Combination compared with simvastatin will reduce the incidence of the composite endpoint of CV death, major coronary events (non-fatal MI, documented unstable angina that requires admission into a hospital, all coronary revascularization with either PCI or CABG occurring at least 30 days after randomization), and non-fatal stroke.

6.2.2 Secondary Hypothesis: To Evaluate Supportive Composite Endpoints

1. In stabilized high-risk ACS subjects, the administration of Ezetimibe/Simvastatin Combination compared with simvastatin will reduce the incidence of the composite endpoint of death due to all causes, major coronary events, and non-fatal stroke.
2. In stabilized high-risk ACS subjects, the administration of Ezetimibe/Simvastatin Combination compared with simvastatin will reduce the incidence of the composite endpoint of CHD death, non-fatal MI, and urgent coronary revascularization with either PCI or CABG occurring at least 30 days after randomization.
3. In stabilized high-risk ACS subjects, the administration of Ezetimibe/Simvastatin Combination compared with simvastatin will reduce the incidence of the composite endpoint of CV death, non-fatal MI, documented unstable angina that requires admission into a hospital, all revascularization (including both coronary and non-coronary) occurring at least 30 days after randomization, and non fatal stroke.

6.2.3 Tertiary Hypotheses

1. To evaluate the clinical benefit of treatment on individual endpoints:

   In stabilized high-risk ACS subjects, the administration of Ezetimibe/Simvastatin Combination compared with simvastatin will reduce the incidence of the following endpoints, each analyzed individually: death from any cause, CHD death, CV death, MI, documented unstable angina that requires admission into a hospital, all coronary revascularization with either PCI or CABG occurring at least 30 days after randomization, urgent coronary revascularization with either PCI or CABG occurring at least 30 days after randomization, all revascularization (including both coronary and non-coronary) occurring at least 30 days after randomization, stroke, any cardiovascular event leading to admission into a hospital, and CHF that requires hospitalization occurring at least 30 days after randomization.
2. To evaluate the proportion of subjects achieving reductions in LDL-C and hs-CRP:
   a. In stabilized high-risk ACS subjects, the administration of Ezetimibe/Simvastatin Combination compared with simvastatin will result in a greater percentage of subjects achieving an LDL-C concentration of <70 mg/dL (<1.8 mmol/L) and hs-CRP concentration of <2.0 mg/L.
   b. In stabilized high-risk ACS subjects, the group of subjects, regardless of treatment, achieving the dual goal of an LDL-C concentration of <70 mg/dL (<1.8 mmol/L) and an hs-CRP concentration of <2.0 mg/L

will reduce the incidence of the primary composite endpoint compared with the group of subjects, regardless of treatment, that do not achieve the dual goal for LDL-C and hs-CRP.

3. To evaluate safety measurements:

   In stabilized high-risk ACS subjects, Ezetimibe/Simvastatin Combination will be well-tolerated.

7.0 INVESTIGATIONAL AND ANALYSIS PLAN

7.1 Overall Study Design and Plan: Description

Refer to Study Design Diagram (**Section 2.1**) and Study Flow Chart (**Section 2.2**).

7.2 Discussion of the Study Design

7.2.1 Design of the Study

This is a randomized, active-control, parallel-group, balanced, multicenter, doubleblind, study of subjects with stabilized high-risk ACS and LDL-C 125 mg/dL (3.2 mmol/L) (or 100 mg/dL [2.6 mmol/L] while receiving statin therapy) 10 days (240 hours) of admittance into a hospital.

7.2.1.1 Subjects

Clinically stable (**Section 7.3.2**), high-risk ACS subjects from the following three categories will be considered for enrollment:

1. Subjects with NSTE-ACS (unstable angina or NSTEMI) participating in the EARLY-ACS Study (Protocol No. P03684):

   Clinically stable subjects enrolled in the EARLY-ACS Study under Protocol No. P03684, a double-blind, randomized, parallel-group study of Integrilin® (eptifibatide) vs placebo in subjects with high-risk non-ST segment elevation ACS non-ST segment elevation ACS (NSTE-ACS unstable angina or NSTEMI), may be eligible to enroll in the current study after completing the 96-hour primary endpoint of the acute segment of EARLY-ACS treatment (the acute segment of EARLY-ACS treatment is the initial phase of administration of randomized treatment with eptifibatide or matching placebo through catheterization).
2. Subjects with NSTE-ACS (unstable angina or NSTEMI) enrolling directly into the current study:

   High-risk NSTE-ACS (unstable angina or NSTEMI) subjects who have been stabilized and are not participating in the EARLY-ACS Study, who qualify in accordance with the entry criteria of the current Protocol No. P04103 may be eligible to enroll in the current study.
3. Subjects with STEMI:

The entry criteria for a high-risk ACS subject are described in **Section 7.3.1**. Events that preclude a subject from being considered clinically stable are described in **Section 7.3.2**.

The study will enroll subjects receiving chronic prescription lipid-lowering treatment and subjects not receiving any chronic prescription lipid-lowering treatment. The criteria defining chronic prescription lipid-lowering therapy are described in **Section 7.3.1** and **Appendix 4**.

7.2.1.2 Randomized Treatment Assignment

Eligible subjects will receive randomized, double-blind treatment assignment in a 1:1 ratio to either Ezetimibe/Simvastatin Combination 10/40 or simvastatin 40 mg QD. Study drug will be administered once daily in the evening. Initially, all subjects will be assigned to receive randomized treatment comprising three tablets as follows:

- One Ezetimibe/Simvastatin Combination 10/40 tablet and two simvastatin 40 mg placebo tablets; or
- One Ezetimibe/Simvastatin Combination 10/40 placebo tablet, one simvastatin 40 mg tablet, and one simvastatin 40 mg placebo tablet.

After randomization subjects will have regularly scheduled visits at the end of Month 1 and Month 4, and every 4 months thereafter (**Section 2.2**).

7.2.1.3 Measuring Clinical Endpoint Events

In this trial a suspected clinical endpoint event is to be reported in the clinical endpoint events module of the eCRF. A suspected clinical endpoint event, regardless of when the event occurs, is not to be reported as an AE or SAE in the eCRF or reported in an expedited manner to the sponsor's Drug Safety Surveillance (DSS) department as an SAE (**Section 7.7.2.2.5**). The CEC will adjudicate each suspected clinical endpoint event according to its guidelines stated in the CEC Manual of Operations (**Section 9.3.2**). The suspected clinical endpoint events are listed below:

Death from any cause, MI, unstable angina, all revascularization (including both coronary and non-coronary), stroke, any CV event leading to hospitalization, and CHF.

The outcomes measures for all efficacy clinical endpoints will be the time from randomized treatment assignment until the first occurrence of each confirmed endpoint event (**Table 5**) for each subject (**Section 7.7.1.1.1**).

7.2.1.4 Duration of Study

The study will continue until each subject has been followed for a minimum of 2.5 years and at least one primary endpoint event (**Section 7.7.1.1.1**) has been documented in a minimum of 5250 subjects. If at least 5250 subjects do not have at least one documented primary endpoint event within 2.5 years of the completion of enrollment, the study will continue until this number of primary endpoint events has accumulated. See **Section 8.5** for a description of the sample size and explanation for the number of primary endpoint events to be accumulated.

The number of subjects reporting primary endpoints may be extended beyond the 5250 planned in order to maintain adequate power in the study. The independent LDL-C Monitoring Committee (LMC) will periodically review the achieved LDL-C results and advise the Executive Group within the Operations Committee regarding potentially increasing the targeted number of primary endpoint events, if the difference in median LDL-C between treatment groups is less than anticipated. See **Section 8.5** for further discussion.

Each subject, including each subject who is discontinued from study medication, will be monitored for any clinical endpoint event until the termination of the study. A subject that reaches a non-fatal suspected clinical endpoint should continue to receive blinded study medication to the end of the trial. The occurrence of a non-fatal suspected clinical endpoint is not a reason for discontinuing study medication.

7.2.2 Participation in and Completion of the Study

A subject is considered to be enrolled in the study when the subject signs the informed consent.

A subject is considered to have completed the study upon the completion of the last protocol-specified visit or contact (eg, phone contact with the investigator or qualified designee).

A subject's participation may be terminated prior to completion for the reasons described in **Section 7.3.3**. For those subjects who do not complete the study, subject participation will be considered terminated upon the completion of the last visit or contact.

Each subject, including each subject who is discontinued from study medication, will be monitored for any clinical endpoint event until the termination of the study.

The study will run until each subject has been followed for a minimum of 2.5 years after being enrolled and at least one primary endpoint event has been documented in at least 5250 subjects. If 5250 subjects do not have at least one documented primary endpoint event within 2.5 years of the completion of enrollment, the study will continue until this number of primary endpoint events has accumulated.

7.3 Study Population

Adult subjects with a diagnosis of high-risk ACS will be selected for the study.
Approximately 18,000 subjects will be assigned randomized treatment at up to 1500 sites worldwide. With this Amendment #***5***, enrollment of new subjects ***has completed***. Subjects must meet all the inclusion criteria and none of the exclusion criteria to receive treatment assignment.

7.3.1 Subject Inclusion Criteria

The subject must meet **ALL** criteria listed below for entry:

1. Subject may be of either sex and of any race.
2. A subject in whom a PCI is planned as management for the qualifying ACS event should undergo PCI prior to Randomization and within the 10-day period after initial hospitalization for the qualifying ACS event. Although subsequent staged PCI procedures are permitted, all planned PCIs that are known at the time of screening must be completed within 30 days of Randomization. Whenever possible, PCI procedures (including staged procedures) known to be indicated at the time of screening should be completed prior to Randomization.
3. Subject must have NSTE-ACS (unstable angina or NSTEMI) according to the following criteria:
   a. A NSTE-ACS (unstable angina or NSTEMI) subject participating in the EARLY-ACS Study (Protocol No. P03684) who has been clinically stabilized (**Section 7.3.2**) will be eligible for entry in the current study under Protocol No. P04103 □10 days (□240 hours) of presenting to the hospital. The subject must complete the 96-hour primary endpoint of the acute segment of EARLY-ACS treatment (the acute segment of EARLY-ACS treatment is the initial phase of administration of randomized treatment with eptifibatide or matching placebo through catheterization) and be clinically stable before enrolling in the current study.

   -OR-

   b. A subject not participating in the EARLY-ACS Study, but who is defined as NSTE-ACS (unstable angina or NSTEMI) by meeting all of the following criteria, and has been clinically stable for at least 24 hours prior to screening/randomization, will be eligible to enter directly into the current study □10 days (□240 hours) of acute admittance into a hospital:
      (1) The subject has experienced symptoms of cardiac ischemia at rest prompting acute care hospitalization with at least one episode lasting at least 10 minutes.
      (2) □50 years of age; and
      (3) Any 1 of the following criteria:
         (a) Electrocardiogram changes characterized by either of the following:
            [1] New or presumably new ST-segment depression □0.1 mV in at least 2 contiguous ECG leads; or
            [2] Transient (<30 minutes) ST-segment elevation □0.1 mV in at least 2 contiguous ECG leads.
         (b) Any of the following cardiovascular biomarkers elevated above the upper limit of normal (ULN):
            [1] Troponin I;
            [2] Troponin T; and/or
            [3] Creatine kinase-MB fraction (CK-MB).
         (c) Diabetes mellitus;
         (d) History of prior MI;

(e) History of peripheral arterial disease;

(f) History of cerebrovascular disease;

(g) History of CABG ≥3 years prior to entry; (Note: This is 1 item in a list of 8 criteria. If the subject has had CABG within the 3 years prior, they still may be eligible if at least one criterion of a–f or h from this list are met.);

(h) Multivessel coronary artery disease previously documented by catheterization (2 or 3 vessels with ≥50% stenosis) including the catheterization performed during the index admission for the qualifying event.

Note: It is strongly recommended that each high-risk NSTE-ACS (unstable angina or NSTEMI) subject not enrolled in the EARLY-ACS study undergo a cardiac catheterization within 72 hours of acute presentation. All study sites will have access to catheterization or other invasive procedures to ensure that all subjects are provided a similar standard of care.

4. Subject must meet the following criteria for LDL-C concentrations at the time of admittance into a hospital (Each measurement of LDL-C performed within the first 24 hours of admittance must meet the criteria):

a. Definition of "chronic prescription lipid-lowering therapy" and "lipid-therapy naïve." (also presented in **Appendix 4**):

(1) A subject is considered to be receiving chronic prescription lipid-lowering therapy if he/she has been receiving any prescription lipid-lowering therapy continuously for >4 weeks prior to and continuing until the qualifying ACS hospital admission.

(2) All other subjects (including those who initiate prescription lipid-lowering therapy after the qualifying ACS hospital admission) are considered to be "lipid-therapy naïve."

(3) To be eligible, a subject receiving chronic prescription lipid-lowering therapy must be receiving therapy with a lipid-lowering potency equal to or less than simvastatin 40 mg QD.

(a) A subject receiving chronic lipid-lowering therapy with LDL-C lowering potency greater than simvastatin 40 mg will not be eligible (Exclusion Criterion 5 in **Section 7.3.2**). The prohibited chronic lipid-lowering therapies are the following: [1] All doses of simvastatin >40 mg;

[2] All doses of atorvastatin ≥40 mg;

[3] All doses of rosuvastatin;

[4] All doses of Ezetimibe/Simvastatin Combination;

[5] Ezetimibe coadministered with any dose of any statin.

(b) For the purposes of this protocol, all other chronic prescription lipid lowering therapies will be considered equal or less potent than simvastatin 40 mg QD and subjects taking such therapies may be considered for enrollment.

b. A lipid-therapy naïve subject will be eligible to enroll if his/her LDL-C concentration is ≥50 mg/dL (≥1.3 mmol/L) and ≥125 mg/dL (≥3.2 mmol/L);

c. A subject receiving chronic prescription lipid-lowering therapy will be eligible to enroll, if his/her LDL-C concentration is ≥50 mg/dL (≥1.3 mmol/L) and ≥100 mg/dL (≥2.6 mmol/L).

d. Observe the following conditions concerning lipid concentrations and experience with chronic prescription lipid-lowering therapy:

(1) Blood lipid levels, including LDL-C, should be measured as close as possible to each subject's presentation to a hospital, but no later than 24 hours after admission. A subject's baseline LDL-

C and lipid-loweringtherapy status are to be based on the subject's status at the time of the initial acute event leading to admittance into a hospital.

(2) The specimens do not need to be obtained after fasting. In addition if the blood lipid levels are not measured at the time of admittance, they may be determined later on blood from the subject that was obtained at the time of admittance into the hospital.

(3) If a recent lipid panel (<6 months prior to presentation) is available, the values may be used for subject screening and determination of eligibility if the subject's therapy had not changed since the lipid measurement and if no specimen was drawn within the first 24 hours after admission to a hospital.

(4) If only a total cholesterol (TC) level is available at the time of admission, the subject will still be eligible if TC concentrations meet the following criteria at the time of admission and repeat lipid measurements (preferred but not obligate fasting) are obtained as soon as possible (preferably within 24 hours of admission) meet the above LDL-C criteria:

(a) TC concentration □190 mg/dL (□4.9 mmol/L) for a lipid-therapy naïve subject;

(b) TC concentration □150 mg/dL (□3.9 mmol/L) for a subject receiving chronic prescription lipid-lowering therapy.

5. Subject must have a plasma triglyceride (TG) level □350 mg/dL (□4.0 mmol/L). A subject found to have a non-fasting TG >350 mg/dL (>4.0 mmol/L) upon admittance into a hospital, but have TG <1500 mg/dL (<17.0 mmol/L), must have TG □350 mg/dL (□4.0 mmol/L) on a fasting specimen obtained as soon as possible (preferably within 24 hours of admission).
6. Subject's clinical laboratory tests must be within reference ranges or clinically acceptable to the investigator/sponsor.
7. At Screening/Randomization each woman of child-bearing potential must agree to use a medically accepted method of contraception while receiving protocolspecified medication and for 6 weeks after stopping the medication. All postmenarchal women who are <2 years menopausal or who have not had surgical sterilization or a hysterectomy are considered to be women of childbearing potential.

   Acceptable methods of contraception include condoms (male or female) with or without a spermicidal agent, diaphragm or cervical cap with spermicide, medically prescribed intrauterine device (IUD), oral or injectable hormonal contraceptive, and surgical sterilization (eg, hysterectomy or tubal ligation).
8. Each woman of child-bearing potential who is not currently sexually active must agree to use a medically accepted method of contraception should she becomes sexually active while participating in the study.

7.3.2 Subject Exclusion Criteria

The subject will be excluded from entry if **ANY** of the criteria listed below are met:

1. Subject who is clinically unstable. A subject is considered clinically unstable if he/she displays any of the following events within 24 hours prior to Screening/Randomization: a. Hemodynamic events:

   (1) Hypotension defined as sustained systolic blood pressure of <90 mmHg due to cardiac failure with associated symptoms;

   (2) Unstable or severe pulmonary edema/decompensated CHF;

(3) Acute mitral regurgitation;

(4) Acute ventricular septal defect.

b. Recurrent symptoms of cardiac ischemia;

c. Stroke or transient ischemic attack (TIA);

d. Arrhythmic events:

(1) Ventricular fibrillation;

(2) Sustained ventricular tachycardia lasting >30 seconds or in association with symptoms;

(3) Complete heart block;

(4) High grade second degree heart block.

2. Subject who plans or undergoes CABG in response to the initial episode of ACS.

3. Subject who must continue to receive treatment that is listed in **Table 2**. These prohibited medications must be stopped at entry and may not be taken during the study after Randomization. There are no washout periods for medications prohibited at entry. However, see the definitions of "chronic prescription lipidlowering therapy" and "lipid-therapy naïve" in **Section 7.3.1**, Criterion 4. The list in **Table 2** identifies therapies prohibited during the current trial in the interests of subject safety and to protect the scientific interests of the study. Refer to the current local labeling for ezetimibe/simvastatin and for simvastatin to obtain a complete list of the respective prohibited concomitant medications.

Table 2 Prohibited Medications for Entry into the Study: Medications That Must Be Stopped at Entry

Protocol No. P04103

Prohibited Medications[a,b]
Probucol
Amiodarone[c]
Cyclosporine
Fibric Acid derivatives (fibrates)
Resins
Niacin, >100 mg/day
Danazol
Antifungal azoles via oral and parenteral administration (itraconazole, fluconazole, and ketoconazole)
Macrolide/Ketolide antibiotics via oral and parenteral administration (eg, clarithromycin, erythromycin, telithromycin) **Note:** azithromycin may be given
Protease inhibitors
Nefazodone
Any investigational drugs
Diltiazem

Verapamil (sustained release formulations)
Verapamil
Grapefruit juice >1 quart/day
Statins
Ezetimibe
Fusidic acid
Torcetrapib, within 1 year prior to Screening/Randomization

[a] Short-term therapy of prohibited medication is acceptable, provided study medication is interrupted during the administration and restarted after short-term therapy is completed.

[b] Any medications not appearing on the above list may be administered during the course of the study.

[c] A course of amiodarone requires a 1 month wait before resuming study drug if 6 grams or more was received by the subject.

4. The investigator feels that discontinuation of existing lipid-lowering regimen poses a risk to the subject.
5. The subject is receiving chronic prescription lipid-lowering therapy with LDL-C lowering potency greater than simvastatin 40 mg (**Appendix 4**).

   Note: If potent prescription lipid-lowering therapy is begun after hospitalization and was not administered chronically prior to hospitalization, then the subject is not to be excluded.
6. Subject has an allergy/sensitivity to any statin, ezetimibe, and/or their excipients.
7. Subject has active liver disease or persistent serum transaminase elevations (≥2 x ULN). A subject with transient increases in serum transaminases due to the index MI may be enrolled.
8. Subject has calculated creatinine clearance (CrCl) <30 mL/min or dialysis within 30 days. Creatinine clearance is to be calculated according to the Cockcroft-Gault equation:

   a. Men: $$CrCl = \frac{(140 - age) * (weight\ in\ kg)}{72 * serum\ creatinine\ in\ mg/dL}$$

   b. Women: $$CrCl = \frac{(140 - age) * (weight\ in\ kg)}{72 * serum\ creatinine\ in\ mg/dL} * 0.85$$

9. Subject has a history of alcohol and/or drug abuse.
10. Subject is a pregnant or lactating woman, or woman intending to become pregnant.

    Note: Each female subject of child-bearing potential must have a serum or urine pregnancy test performed by the local laboratory at Screening/Randomization and the results of the pregnancy test must be negative (not pregnant) prior to randomization.

11. Subject with any clinically significant condition or situation, other than the condition being studied that, in the opinion of the investigator, would interfere with the study evaluations or optimal participation in the study.
12. Subject who has used any investigational drugs within 30 days of Screening/Randomization.
13. Subject who is participating in any other clinical study involving an investigational drug or device with the following exceptions:
    a. A subject participating in the EARLY-ACS Study (Protocol No. P03684) is not necessarily to be excluded.
    b. A subject participating in clinical research of approved therapy being administered according to the therapy's labeled use is not to be excluded.
14. Subject with prior enrollment in this current study (Protocol No. P04103).
15. Subject who is part of the staff personnel directly involved with this study.
16. Subject who is a family member of the investigational study staff.

7.3.3 Subject Discontinuation Criteria From Study Medication

Study drug administration may be interrupted temporarily for a subject for such reasons as the administration of a short course of a prohibited medication as described in **Table 3**, elevations in ALT and/or AST as described in **Section 7.6.4.1**, elevations in CPK as described in **Section 7.6.4.2**, the occurrence of suspected clinical endpoint events, or other observations related to safety. A subject who has treatment with study drug interrupted temporarily may resume the assigned study drug at the discretion of the investigator, provided that the resumption of study drug does not pose an undue hazard to the subject.

Each subject, including each subject who is discontinued from study medication will be monitored for any clinical endpoint event until the termination of the study (**Section 7.6.5**).

A subject that reaches a non-fatal suspected clinical endpoint (**Table 5**) should continue to receive blinded study medication to the end of the trial. The occurrence of a non-fatal suspected clinical endpoint is not a reason for discontinuing study medication.

A subject may be discontinued from study medication during the study for any of the following reasons:

1. Serious or life-threatening adverse event in which the condition exposes the subject to significant risk by continuing in the study or will interfere with the subject's ability to adhere to the requirements of the protocol (**Section 7.7.2.2.1** and **Section 7.7.2.2.5**);
2. Request of the subject (subjects have the right to discontinue treatment at any time for any reason);
3. Pregnancy;
4. Two episodes of consecutive observations of AST and/or ALT □3 x ULN (**Section 7.6.4.1**).
5. Adverse event of myopathy or rhabdomyolysis documented with elevations in CPK as specified in **Section 7.6.4.2**.
6. ***LDL-C concentration ≥100 mg/dL (>2.6 mmol/L) at 2 consecutive observations. Subjects meeting this criterion should be discontinued from study medication to allow for medical management (with open-label lipidlowering therapies generally including administration of***

a more powerful statin) at the discretion of the treating physician. These subjects should continue all follow-up requirements of the trial.

7. Long-term need for prohibited concomitant medication (**Table 2**).
8. Need for permanent dialysis and/or chronic renal failure with CrCl 30 ml/min.

It is the right and the duty of the investigator or subinvestigator to interrupt treatment of any subject if he/she feels that discontinuation from study medication is necessary to protect the subject, or that there are unmanageable factors, that may interfere significantly with the study procedures and/or the interpretation of results.
If a subject discontinues study medication prior to completion of the study, the reason for the discontinuation will be obtained. The date of the last dose of study medication and the date of the last assessment and/or contact will be obtained. This information will be documented in the appropriate section of the eCRF. A follow-up contact (telephone or visit) will be arranged as appropriate.

At the time of discontinuation, every effort should be made to ensure all procedures and evaluations scheduled for the final study visit are performed (**Section 2.2**, Study Flow Chart and **Section 7.5**, Study Schedule). The reason for discontinuation of study medication by a subject should be recorded in the source documentation for that subject. For all discontinued subjects, adverse events should be recorded and medication compliance should be assessed. Any returned drug should be inventoried.

7.3.4 Replacement of Subjects

Subjects who discontinue treatment early will not be replaced.

7.4 Treatments

7.4.1 Study Treatments

7.4.1.1 Treatments Administered

7.4.1.1.1 Randomized Treatment Assignment

All subjects who meet the entry criteria will be assigned to receive randomized treatment in one of the two treatment groups in a 1:1 ratio. Treatment will comprise three tablets as follows:

- Ezetimibe/Simvastatin Combination Treatment Group: One Ezetimibe/Simvastatin Combination 10/40 tablet and two simvastatin 40 mg placebo tablets; or
- Simvastatin Treatment Group: One Ezetimibe/Simvastatin Combination 10/40 placebo tablet, one simvastatin 40 mg tablet, and one simvastatin 40 mg placebo tablet.

For clarity regarding the changes to drug dosing in this Amendment #5, the following section reviews the current protocol procedure for drug allotment.

Treatment is provided in 3 bottles: Bottle A, Bottle B, and Bottle C. Subjects are to take 1 tablet from each bottle once each day in the evening. At the time of treatment assignment, medications in the bottles were as follows:

- ***For subjects assigned to receive Ezetimibe/Simvastatin 10/40: Bottle A contained Ezetimibe/Simvastatin Combination 10/40 tablets. Bottle B and Bottle C each contained matching placebo tablets for Simvastatin 40 mg;***

- ***For subjects assigned to receive simvastatin 40 mg: Bottle A contained matching placebo tablets for Ezetimibe/Simvastatin Combination 10/40 tablets. Bottle B contained simvastatin 40 mg tablets. Bottle C contained matching placebo tablets for Simvastatin 40 mg.***

7.4.1.1.2 Increasing Simvastatin Dose

Earlier in the trial, prior to this current amendment #5, if a subject had 2 consecutive LDL-C measurements >79 mg/dL (>2.0 mmol/L), that subject was to have his/her simvastatin dose increased to 80 mg in a double-blind manner at the next regularly scheduled visit. To achieve the increase in the simvastatin dose to 80 mg without unblinding treatment, a simvastatin 40 mg tablet replaced a simvastatin 40 mg placebo tablet in the dosing regimen Bottle C. To avoid alerting investigators to subjects receiving a total dose of simvastatin 80 mg QD, "dummy titration" subjects were called at random from across the whole study. The ratio of subjects with LDL-C >79 mg/dL (>2.0 mmol/L) to dummy titration subjects was 2:1.

Thus, for subjects who had the dose of simvastatin increased to 80 mg, medications in the bottles were as follows:

- ***For subjects originally assigned to receive Ezetimibe/Simvastatin 10/40, but were to increase the simvastatin component to 80 mg: Bottle A contained Ezetimibe/Simvastatin Combination 10/40 tablets. Bottle B contained matching placebo tablets for simvastatin 40 mg. Bottle C contained simvastatin 40 mg tablets.***

- ***For subjects originally assigned to receive simvastatin 40 mg, but were to increase the simvastatin dose to 80 mg: Bottle A contained matching placebo tablets for Ezetimibe/Simvastatin Combination 10/40 tablets. Bottle B contained simvastatin 40 mg tablets. Bottle C contained simvastatin 40 mg tablets.***

"Dummy titration" subjects did not have their medication altered.

With this amendment #5, use of simvastatin 80 mg in the study is modified:

- ***No additional subjects will have their simvastatin dose increased to 80 mg;***
- ***Subjects already receiving study medication that includes a simvastatin dose of 80 mg will have their medications reevaluated;***
- ***See Section 7.6.3 for a description of how subjects receiving simvastatin 80 mg will be managed.***

7.4.1.2 Method of Treatment Assignment, Randomization, and/or Stratification

At randomization, subjects will be assigned a randomization number corresponding to an initial treatment group according to their sequential entrance into the study. This randomization number is determined by a computer-generated random code. It will be provided to the study site by the central randomization service at the time the subject receives randomized treatment assignment. Treatment should be started as close as possible to the date in which randomized treatment is assigned, preferably on the same day.

Randomized treatment assignment for this study will be stratified by the following three factors to obtain balance across the treatment groups:

- Randomized treatment assignment for subjects entering the current study (P04103) from the EARLY-ACS study (P03684): assigned eptifibatide or placebo;
- Experience with lipid-lowering therapy (**Appendix 4**): subjects receiving chronic prescription lipid-lowering therapy for >4 weeks prior to and continuing until the admittance into a hospital or subjects not receiving chronic prescription lipidlowering therapy. Enrollment of subjects receiving chronic prescription lipidlowering therapy will be limited to 50% of all subjects within each country;
- High-risk ACS diagnosis: NSTE-ACS (unstable angina or NSTEMI) or STEMI.

No further stratification of randomized treatment assignment based on age, sex, or other characteristics will be performed.

7.4.1.3 Selection and Timing of Dose for Each Subject

All subjects will be dosed with study drug (Ezetimibe/Simvastatin Combination, simvastatin, and/or matching placebo, as appropriate) in the evening, consistent with the Ezetimibe/Simvastatin Combination label and simvastatin label.

7.4.1.4 Blinding of Study Treatments

This is a double-blind study; neither the investigator, sponsor, nor the subject will know the content of the bottles. The randomization schedule for blinding of treatments will be maintained by the sponsor, provided to the central randomization service, and disclosed only after study completion and database closure.

Unblinding should occur only in the event of an emergency or adverse event for which it is necessary to know the study treatment to determine an appropriate course of therapy for the subject. If the investigator must identify the treatment assignment of an individual subject, the investigator or qualified designee is to call the TIMI Hotline. The TIMI Hotline will contact the Central randomization Center. Unblinding performed by the Central Randomization Center at the request of the investigator is to be reported in writing by the investigator to the sponsor, including a written explanation of the reason why the blind was broken.

7.4.1.5 Investigational Products

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, handling, storage, distribution, and usage of these materials in accordance with the protocol and any applicable laws and regulations.

7.4.1.5.1 Identity of Investigational Products

Ezetimibe/Simvastatin Combination 10/40 tablet (SCH 465981, under the brand “VYTORIN” or “INEGY” in some regions) is formulated to contain a fixed dose of ezetimibe 10 mg with simvastatin 40 mg. In addition to the ezetimibe and simvastatin, each tablet also contains the following commonly used inactive excipients: microcrystalline cellulose, citric acid, butylated hydroxyanisole, propyl gallate, and magnesium stearate. The Ezetimibe/Simvastatin Combination 10/40 tablet and matching placebo (identical in appearance to the Ezetimibe/Simvastatin Combination 10/40 tablet) are manufactured by Merck & Co., Inc. and will be provided to the study administrator.

The simvastatin 40 mg tablet and matching placebo (identical in appearance to simvastatin 40 mg tablet) are manufactured by Merck & Co., Inc. and will be provided to the study administrator.

Blinded study medication will consist of three tablets, identified as Study Medication A, Study Medication B, and Study Medication C. All study medication is to be labeled as described in **Section 7.4.1.5.3** and packaged as described in **Section 7.4.1.5.4**. Study Medication A comprises oval, white tablets. Study Medication B and Study Medication C comprise pink, round tablets.

7.4.1.5.2 Source

All study medication will be manufactured by Merck & Co., Inc, and will be provided to the investigators by the study administrator.

7.4.1.5.3 Labeling

The label will contain the study number, Clinical Material Packaging Request number (PR), Treatment Unit Number, a space for insertion of the subject's randomization number. Each dose of study medication will consist of three tablets, one tablet from Bottle A, one tablet from Bottle B and one tablet from Bottle C. Each bottle will be labeled with the instructions as follows:

- Instructions on Bottle A will be: "Take one tablet from Bottle A every evening."
- Instructions on Bottle B will be: "Take one tablet from Bottle B every evening."
- Instructions on Bottle C will be: "Take one tablet from Bottle C every evening."

7.4.1.5.4 Packaging

Subject Treatment Units will be packaged according to a computer generated random code. Subject Treatment Units will be placed at the center prior to the first subject being randomized. Additional units will be forwarded to the center as needed based on the number of subjects randomized and retained on drug in the study.
Each Subject Treatment Unit will contain adequate drug to manage the subject for 4 months on study:

- At each study visit a subject will receive two treatment units: the first treatment unit will contain two Bottle A's and two Bottle B's and the second treatment unit will contain two Bottle C's. Bottle A will contain Ezetimibe/Simvastatin Combination 10/40 or matching placebo. Each of Bottle B and Bottle C will contain simvastatin 40 mg or matching placebo. All bottles will contain 70 tablets, which is an adequate drug supply for 2 month of dosing. Each dose will consist of three tablets, one tablet from Bottle A, one tablet from Bottle B and one tablet from Bottle C, to be taken every evening.

7.4.1.5.5 Storage

Study drug supplies must be stored at room temperature in a secure, limited-access location under the storage conditions specified on the drug supply label.

7.4.1.5.6 Dispensing

The investigator agrees neither to dispense the study drug from, nor store it at any site(s) other than those listed on the Form FDA 1572. The investigator agrees that study drug(s) will be dispensed by the investigator or subinvestigator(s) named on the Form FDA 1572, or their qualified designees. The investigator, subinvestigators, or qualified designees also agree that the study drug(s) will be dispensed only to study subjects who have provided written informed consent, have met all entry criteria, and been assigned randomized treatment via the IVRS. Clinical supplies may not be used for any purpose other than that stated in the protocol.

Once the subject is considered qualified for entry into the study, the study site is to contact the Central Randomization Center and receive a subject randomization number and the numbers of the initial two treatment unit assignments. As described in **Section 7.4.1.5.4**, the first treatment unit will contain two Bottle A's and two Bottle B's and the second treatment unit will contain two Bottle C's.

The Central Randomization Center will assign the subject randomization number according to the subject's sequential entry into the study. The subject will be identified by this subject randomization number for the duration of the study and in the reporting of results of the study.

At each study visit, the study site will contact the Central Randomization Center, which will assign two additional treatment units to the subject, the first treatment unit will contain two Bottle A's and two Bottle B's and the second treatment unit will contain two Bottle C's, as described in **Section 7.4.1.5.4**.

This is a double-blind study; the investigator, sponsor, nor subject will know the content of the bottles.

7.4.1.5.7 Replacement Units

If a subject's treatment unit is lost or destroyed, the study site should be informed as soon as possible. The study site will contact the Central Randomization Center, which will assign an additional treatment unit. The replacement treatment unit should be retired at the next scheduled study visit, regardless of the number of tablets utilized.

7.4.1.5.8 Drug Accountability

Subjects will be instructed to return all unused and partially used test articles at all protocol-specified visits for drug inventory and assessment of subject compliance.

An accurate and current accounting of the dispensing and return of study drug(s)for each subject will be maintained on an ongoing basis by a member of the study site staff in a test article accountability ledger (TAAL) and will be verified by the sponsor's study monitor.

All drug supplies, including all containers of study drug, whether empty or containing unused study drug, must be returned to the sponsor or its designee, unless investigators are instructed otherwise by the sponsor or its designee. The sponsor's study monitor will provide instructions on the return of all drug supplies. A final inventory of the total amount of drug received at each study site against the amount used and returned must be recorded in the Test Article Summary Inventory Record (TASIR) or an equivalent document.

Inventory records must be readily available for inspection by the study monitor and/or auditor, and open to government inspection at any time.

7.4.2 Nonstudy Treatments

7.4.2.1 Prior and Concomitant Medications

Cardiovascular-related medication taken chronically by the subject at the time of the initial ACS event prompting hospitalization and before starting the study and cardiovascular-related concomitant therapy taken

by the subject during the study are to be recorded on the eCRF. During the trial, concomitant medication prescribed in response to an SAE are to be recorded on the eCRF. The use of any concomitant medication must relate to an adverse event or the subject's medical history.

7.4.2.1.1 Medications Prohibited at Screening/Randomization and During the Study

The medications that must be discontinued at Screening/Randomization are listed in **Table 2** in Section 7.3.2 with the subject exclusion criteria.

The subject must not take the treatments listed in **Table 3** during the study after Randomization.

Table 3 Medications Prohibited During the Study

Protocol No. P04103

Prohibited Medications[a,b]
Probucol
Amiodarone[c]
Cyclosporine
Fibric Acid derivatives (fibrates)
Ezetimibe
Resins
Statins
Niacin, >100 mg/day
Danazol
Antifungal azoles via oral and parenteral administration (itraconazole, fluconazole and ketoconazole)
Macrolide/Ketolide antibiotics via oral and parenteral administration (eg, clarithromycin, erythromycin, telithromycin). Azithromycin is not prohibited
Protease inhibitors
Nefazodone
Any investigational drugs

Table 3 Medications Prohibited During the Study

Protocol No. P04103

Prohibited Medications[a,b]

Diltiazem
Verapamil (sustained release formulations)
Verapamil
New use of amlodipine[d]
New use of ranolazine[d]
Fusidic acid
Grapefruit juice >1 quart/day
Torcetrapib

[a] Short-term therapy of prohibited medication is acceptable, provided study medication is interrupted during the administration and restarted after short-term therapy is completed.

[b] Any medications not appearing on the above list may be administered during the course of the study.

[c] A course of amiodarone requires a 1 month wait before resuming study drug if 6 grams or more was received by the subject.

[d] ***New use of amlodipine or ranolazine is strongly discouraged. Subjects should not be started on amlodipine or ranolazine if at all possible; rather, alternative therapies should be used. If the subject is already on one of these therapies and is unable to switch to an alternative, or if the subject has no alternative but to start one of these therapies, then the dose of simvastatin cannot exceed 40 mg. See Section 7.6.6 for a description of managing concomitant use of study medication and amlodipine or ranolazine.***

The list in **Table 3** identifies medications prohibited during the current trial in the interests of subject safety and to protect the scientific interests of the study. Refer to the current local labeling for ezetimibe/simvastatin and for simvastatin to obtain a complete list of the respective prohibited concomitant medications.

7.4.2.1.2 Medications Allowed During the Study

Medications not specified as prohibited are to be allowed during the study.

7.4.2.2 Other Treatments

None.

7.4.3 Procedures for Monitoring Subject Compliance

At all protocol-specified visits, the investigator or qualified designee is to note in the appropriate section of the eCRF whether treatment had been taken per protocol in the preceding interval. If not, the date(s) and reason for each deviation must be recorded. Space is provided on the eCRF for explanatory comments. In addition, the study staff will maintain an ongoing record of the dispensing and return of all study medication for each

subject on the TAAL that will be verified by the sponsor's study monitor. Adherence to treatment will be assessed by tablet and bottle card count at each visit. Every effort will be made to maintain adherence as close as possible to 100%. If a subject is found to have reduced compliance, center personnel should make contact with subject on a regular basis to remind him/her to take the study medication.

Subject adherence to treatment will be calculated based upon the study medication the subject has been instructed to take. If the subject was instructed to stop taking study medication from Bottle C in accordance with the conditions described in Section 7.6.3 "Managing Subjects Receiving Simvastatin 80 mg" or Section 7.6.6 "Managing Concomitant Use of Study Medication and Amlodipine or Ranolazine," then adherence to treatment for that subject will be assessed based upon the treatment in Bottle A and Bottle B.

7.5 Study Schedule

An overview of the study is provided in the Study Design Diagram in **Section 2.1**, and the study schedule is shown in the Study Flow Chart in **Section 2.2**. The timing of each visit is relative to randomization (Day 1). These activities and assessments must be made by the investigator or, where appropriate, by a qualified health professional as designated by the investigator.

Blood samples for laboratory tests are to be taken prior to study drug administration at each visit.

The sponsor has specified a schedule of intervals relative to the day of randomized treatment assignment for return visits to the clinic with a "window" of days around each scheduled visit. The sponsor strongly requests that subjects return for clinic visits as close to the specified interval as possible, and preferably within the defined window. If it is not possible for the subject to return within the visit window, then the visit should be scheduled as close to the interval as is convenient for the subject and study site. The recommended visit window is indicated for each visit.

Every effort should be made to ensure that subjects are able to provide a 12-hour fasting sample, but samples are to be collected at each scheduled visit as indicated, regardless of the fasting-state of the subject.

7.5.1 Screening/Randomization (Day 1)

Blood lipids, including LDL-C, should be measured as close as possible to each subject's presentation to a hospital. A subject's baseline LDL-C (used to confirm a subject's eligibility) and lipid-lowering-therapy status (used to answer IVRS questions regarding stratification) are to be based on the subject's status at the time of the initial acute event leading to admittance into a hospital, rather than on the results of the Extended Lipid Panel performed on Day 1.

The following assessments should be performed to confirm subject eligibility before the subject receives randomized treatment assignment to study drug:

1. Explain the study to the subject and obtain written informed consent.
2. Obtain a complete medical history including records from hospital admission for acute episode.
3. Review the Inclusion/Exclusion Criteria and record applicable concomitant medications in the source documentation and transcribe to the appropriate section of the eCRF.

4. Perform an assessment consisting of measurements of blood pressure, pulse, body weight and height, directed physical examination, and waist circumference. These assessments may be performed by a qualified health professional.
5. Calculate the creatinine clearance (**Section 7.3.2**, Criterion 8).
6. Have the local laboratory perform serum or urine pregnancy test on female subjects of child-bearing potential to determine eligibility.
7. Obtain blood samples for the following laboratory evaluations. The samples may be collected by a qualified health professional designated by the investigator. Every effort should be made to ensure that subjects are able to provide a 12-hour fasting sample, but samples are to be collected at each scheduled visit as indicated, regardless of the fasting-state of the subject: a. Extended Lipid Panel;
   b. Extended Safety Panel and CPK will be measured at Screening/Randomization;
   c. Plasma for hs-CRP;
   d. Blood for cardiovascular biomarker analyses – up to 10 mL of plasma and 10 mL of serum for measurement of cardiovascular biomarkers of risk. The 10 mL sample of plasma will be divided into three aliquots of equal volume; the first aliquot is to be distributed to Duke Clinical Research Institute (DCRI), the second aliquot to TIMI, and the third aliquot to the Sponsor. Similarly, the 10 mL sample of serum will be divided into three aliquots of equal volume; the first aliquot is to be distributed to Duke Clinical Research Institute (DCRI), the second aliquot to TIMI, and the third aliquot to the Sponsor.
8. Explain to the subjects that participation in the pharmacogenomics analyses is optional. Subjects who do not consent for this DNA collection may still participate in the IMPROVE-IT Study. Subjects must provide a separate written informed consent for DNA collection and storage and if the health authorities, ethics committee and study center are in agreement. See **Section 7.7.3** for a description of the DNA collection and storage and pharmacogenomic informed consent.

   Discuss the collection and storage of DNA for possible pharmacogenomic analysis and obtain informed consent. This process must be repeated if the subject elects to participate in this analysis at a later visit while enrolled in the study.

   Collect blood sample for DNA extraction and storage. The sample may be collected by a qualified health professional designated by the investigator. The blood sample may be collected at a later visit, provided the subject is fully informed of the collection and storage procedures and separate informed consent is obtained prior to specimen collection.
9. Upon determining that the subject meets all eligibility criteria, the study site is to contact the Central Randomization Center using the Interactive Voice Response System (IVRS). The study center must be prepared to answer questions regarding the following;
   a. Subject's prior early use of eptifibatide;
   b. Subject's prior chronic prescription lipid-lowering therapy experience; and
   c. Subject's ACS diagnosis.

   The IVRS will supply the subject's randomization number which will be used for the duration of the study and the subject's initial treatment unit assignment.
10. Perform quality of life assessment (**Appendix 3**).
11. Dispense subject Treatment Unit and instruct subject regarding evening dosing with study medication. Treatment should be started as close as possible to the date in which randomized treatment is assigned, preferably on Day 1.
12. Schedule next study visit in 1 month. (The timing of each visit is relative to randomized treatment assignment, Day 1. Every effort must be made to have subjects appear at the scheduled visit, but the visit

schedules must accommodate the availability of subjects and study sites. The recommended window is 7 days for the next visit). The appointment should be made so that a blood sample can be obtained from the subject after a 12-hour fast.

Month

7.5.2 1 Visit (□7 Days)

1. Obtain blood samples for laboratory evaluations. The sample may be collected by a qualified health professional designated by the investigator. Every effort should be made to ensure that subjects are able to provide a 12-hour fasting sample, but samples are to be collected at each scheduled visit as indicated, regardless of the fasting-state of the subject: a. Abbreviated Lipid Panel;
   b. Abbreviated Safety Panel;
   c. Pregnancy test (all female subjects of childbearing potential);
   d. Plasma for hs-CRP analysis;
   e. Blood for cardiovascular biomarker analyses – up to 10 mL of plasma and 10 mL of serum for measurement of cardiovascular biomarkers of risk. The 10 mL sample of plasma will be divided into three aliquots of equal volume; the first aliquot is to be distributed to Duke Clinical Research Institute (DCRI), the second aliquot to TIMI, and the third aliquot to the Sponsor. Similarly, the 10 mL sample of serum will be divided into three aliquots of equal volume; the first aliquot is to be distributed to Duke Clinical Research Institute (DCRI), the second aliquot to TIMI, and the third aliquot to the Sponsor.
2. Record adverse events (including concomitant illnesses) and concomitant medications. Record any clinical procedures associated with adverse events. Include questioning for the occurrence of unexplained muscle symptoms.
3. Perform a clinic visit assessment consisting of measurements of blood pressure, pulse, and body weight. The assessment may be performed by a qualified health professional designated by the investigator.
4. Interview the subject regarding medication compliance and inventory the drug returned by the subject to confirm the subject's reported compliance.
   Re-dispense unused drug, because the initial Treatment Unit is to be utilized until the Month 4 visit. The assessment may be performed by a qualified health professional designated by the investigator.
5. Perform pharmacoeconomic assessment and quality of life assessment (**Appendix 3**).
6. Schedule next visit. Every effort must be made to have subjects appear at the scheduled visit, but the visit schedules must accommodate the availability of subjects and study sites. The recommended window is □14 days for the next visit. The appointment should be made so that a blood sample can be obtained from the subject after a 12-hour fast. Explain to the subject that a between-visit blood draw may be scheduled at the end of Month 2 (or sooner, if safety is an issue), based on the results of the assessment from the Month 1 Visit.

7.5.3 4, Month 8 Visits (□14 Days) Only

1. Obtain blood samples for the laboratory evaluations. The samples may be collected by a qualified health professional designated by the investigator. Every effort should be made to ensure that subjects are able to provide a 12-hour fasting sample, but samples are to be collected at each scheduled visit as indicated, regardless of the fasting-state of the subject: a. Abbreviated Lipid Panel.
   b. Abbreviated Safety Panel.
   c. Pregnancy test (all female subjects of childbearing potential);
   d. Plasma for hs-CRP analysis.

Month

e. Blood for cardiovascular biomarker analyses – up to 10 mL of plasma and 10 mL of serum for measurement of cardiovascular biomarkers of risk. The 10 mL sample of plasma will be divided into three aliquots of equal volume; the first aliquot is to be distributed to Duke Clinical Research Institute (DCRI), the second aliquot to TIMI, and the third aliquot to the Sponsor. Similarly, the 10 mL sample of serum will be divided into three aliquots of equal volume; the first aliquot is to be distributed to Duke Clinical Research Institute (DCRI), the second aliquot to TIMI, and the third aliquot to the Sponsor.

2. Record adverse events (including concomitant illnesses) and concomitant medications. Record any clinical procedures associated with adverse events. Include questioning for the occurrence of unexplained muscle symptoms.
3. Perform a clinic visit assessment consisting of measurements of blood pressure, pulse, and body weight. The assessment may be performed by a qualified health professional designated by the investigator.
4. Perform pharmacoeconomic assessment and quality of life assessment (**Appendix 3**).
5. Interview the subject regarding medication compliance and inventory the drug returned by the subject to confirm subject's reported compliance. The assessment may be performed by a qualified health professional designated by the investigator.
6. Contact the Central Randomization Center to obtain the number of the Treatment Unit to be dispensed to the subject. Dispense proper treatment unit and instruct subject to start treatment with new treatment unit immediately.
7. Schedule the next visit to occur in 4 months. Every effort must be made to have subjects appear at the scheduled visit, but the visit schedules must accommodate the availability of subjects and study sites. The recommended window is □14 days for the next visit. The appointment should be made so that a blood sample can be obtained from the subject after a 12-hour fast. Explain to the subject that a between-visit blood draw may be scheduled 2 months hence (or sooner, if safety is an issue), based on the results of the assessment from this current visit.

7.5.4 12 Visit (□14 Days) Only

1. Perform a clinic visit assessment consisting of measurements of blood pressure, pulse, body weight, directed physical examination, and waist circumference. The assessment may be performed by a qualified health professional designated by the investigator.
2. Obtain blood samples for the following laboratory evaluations, performed in place of the Abbreviated Lipid Panel and Abbreviated Safety Panel. The samples may be collected by a qualified health professional designated by the investigator. Every effort should be made to ensure that subjects are able to provide a 12-hour fasting sample, but samples are to be collected at each scheduled visit as indicated, regardless of the fasting-state of the subject: a. Extended Lipid Panel;

b. Extended Safety Panel;

c. Pregnancy test (all female subjects of childbearing potential);

d. Plasma for hs-CRP analysis.

e. Blood for cardiovascular biomarker analyses – up to 10 mL of plasma and 10 mL of serum for measurement of cardiovascular biomarkers of risk. The 10 mL sample of plasma will be divided into three aliquots of equal volume; the first aliquot is to be distributed to Duke Clinical Research Institute (DCRI), the second aliquot to TIMI, and the third aliquot to the Sponsor. Similarly, the 10 mL sample of serum will be divided into three aliquots of equal volume; the first

Month

aliquot is to be distributed to Duke Clinical Research Institute (DCRI), the second aliquot to TIMI, and the third aliquot to the Sponsor.

3. Record adverse events (including concomitant illnesses) and concomitant medications. Record any clinical procedures associated with adverse events. Include questioning for the occurrence of unexplained muscle symptoms.
4. Perform pharmacoeconomic assessment and quality of life assessment (**Appendix 3**).
5. Interview the subject regarding medication compliance and inventory the drug returned by the subject to confirm subject's reported compliance. The assessment may be performed by a qualified health professional designated by the investigator.
6. Contact the Central Randomization Center to obtain the number of the Treatment Unit to be dispensed to the subject. Dispense proper treatment unit and instruct subject to start treatment with new treatment unit immediately.
7. Schedule the next visit to occur in 4 months. Every effort must be made to have subjects appear at the scheduled visit, but the visit schedules must accommodate the availability of subjects and study sites. The recommended window is ±14 days for the next visit. The appointment should be made so that a blood sample can be obtained from the subject after a 12-hour fast. Explain to the subject that a between-visit blood draw may be scheduled 2 months hence (or sooner, if safety is an issue), based on the results of the assessment from this current visit.

7.5.5 Month 16 Visit (□14 Days) Only

1. Obtain blood samples for the laboratory evaluations. The samples may be collected by a qualified health professional designated by the investigator. Every effort should be made to ensure that subjects are able to provide a 12-hour fasting sample, but samples are to be collected at each scheduled visit as indicated, regardless of the fasting-state of the subject: a. Abbreviated Lipid Panel.
   b. Abbreviated Safety Panel.
   c. Pregnancy test (all female subjects of childbearing potential);
2. Record adverse events (including concomitant illnesses) and concomitant medications. Record any clinical procedures associated with adverse events. Include questioning for the occurrence of unexplained muscle symptoms.
3. Perform a clinic visit assessment consisting of measurements of blood pressure, pulse, and body weight. The assessment may be performed by a qualified health professional designated by the investigator.
4. Perform pharmacoeconomic assessment and quality of life assessment (**Appendix 3**).
5. Interview the subject regarding medication compliance and inventory the drug returned by the subject to confirm subject's reported compliance. The assessment may be performed by a qualified health professional designated by the investigator.
6. Contact the Central Randomization Center to obtain the number of the Treatment Unit to be dispensed to the subject. Dispense proper treatment unit and instruct subject to start treatment with new treatment unit immediately.
7. Schedule the next visit to occur in 4 months. Every effort must be made to have subjects appear at the scheduled visit, but the visit schedules must accommodate the availability of subjects and study sites. The recommended window is □14 days for the next visit. The appointment should be made so that a blood sample can be obtained from the subject after a 12-hour fast. Explain to the subject that a between-visit blood draw may be scheduled 2 months hence (or sooner, if safety is an issue), based on the results of the assessment from this current visit.

7.5.6 Subsequent 4 Month Visits (□14 Days)

The visits described in this section are those to be scheduled after the Month 16 Visit starting with the Month 20 Visit.

1. Perform urine pregnancy test (all female subjects of childbearing potential);
2. Record adverse events (including concomitant illnesses) and concomitant medications. Record any clinical procedures associated with adverse events. Include questioning for the occurrence of unexplained muscle symptoms.
3. Perform a clinic visit assessment consisting of measurements of blood pressure, pulse, and body weight. The assessment may be performed by a qualified health professional designated by the investigator.
4. Perform pharmacoeconomic assessment and quality of life assessment (**Appendix 3**).
5. Interview the subject regarding medication compliance and inventory the drug returned by the subject to confirm subject's reported compliance. The assessment may be performed by a qualified health professional designated by the investigator.

6. Contact the Central Randomization Center to obtain the number of the Treatment Unit to be dispensed to the subject. Dispense proper treatment unit and instruct subject to start treatment with new treatment unit immediately.
7. Schedule the next visit to occur in 4 months. Every effort must be made to have subjects appear at the scheduled visit, but the visit schedules must accommodate the availability of subjects and study sites. The recommended window is 14 days for the next visit. The appointment should be made so that a blood sample can be obtained from the subject after a 12-hour fast. Explain to the subject that a between-visit blood draw may be scheduled 2 months hence (or sooner, if safety is an issue), based on the results of the assessment from this current visit.

7.5.7 Subsequent Annual Visits (14 Days) Only

Annual Visits occur on the anniversary of the subject's Screening/Randomization Visit.

1. Perform a clinic visit assessment consisting of measurements of blood pressure, pulse, body weight, directed physical examination, and waist circumference. The assessment may be performed by a qualified health professional designated by the investigator.
2. Obtain blood samples for the following laboratory evaluations, performed in place of the Abbreviated Lipid Panel and Abbreviated Safety Panel. The samples may be collected by a qualified health professional designated by the investigator. Every effort should be made to ensure that subjects are able to provide a 12-hour fasting sample, but samples are to be collected at each scheduled visit as indicated, regardless of the fasting-state of the subject: a. Extended Lipid Panel;
   b. Extended Safety Panel;
   c. Plasma for hs-CRP analysis.
   d. Blood for cardiovascular biomarker analyses – up to 10 mL of plasma and 10 mL of serum for measurement of cardiovascular biomarkers of risk. The 10 mL sample of plasma will be divided into three aliquots of equal volume; the first aliquot is to be distributed to Duke Clinical Research Institute (DCRI), the second aliquot to TIMI, and the third aliquot to the Sponsor. Similarly, the 10 mL sample of serum will be divided into three aliquots of equal volume; the first aliquot is to be distributed to Duke Clinical Research Institute (DCRI), the second aliquot to TIMI, and the third aliquot to the Sponsor.
3. Perform urine pregnancy test (all female subjects of childbearing potential).
4. Record adverse events (including concomitant illnesses) and concomitant medications. Record any clinical procedures associated with adverse events. Include questioning for the occurrence of unexplained muscle symptoms.
5. Perform pharmacoeconomic assessment and quality of life assessment (**Appendix 3**).
6. Interview the subject regarding medication compliance and inventory the drug returned by the subject to confirm subject's reported compliance. The assessment may be performed by a qualified health professional designated by the investigator.

7. Contact the Central Randomization Center to obtain the number of the Treatment Unit to be dispensed to the subject. Dispense proper treatment unit and instruct subject to start treatment with new treatment unit immediately.
8. Schedule the next visit to occur in 4 months. Every effort must be made to have subjects appear at the scheduled visit, but the visit schedules must accommodate the availability of subjects and study sites. The recommended window is 14 days for the next visit. The appointment should be made so that a blood sample can be obtained from the subject after a 12-hour fast. Explain to the subject that a between-visit blood draw may be scheduled 2 months hence (or sooner, if safety is an issue), based on the results of the assessment from this current visit.

7.5.8 Final Visit at Completion of the Trial

1. Perform a clinic visit assessment consisting of measurements of blood pressure, pulse, body weight, directed physical examination, and waist circumference. The assessment may be performed by a qualified health professional designated by the investigator.
2. Obtain blood samples for the following laboratory evaluations, performed in place of the Abbreviated Lipid Panel and Abbreviated Safety Panel. The samples may be collected by a qualified health professional designated by the investigator. Every effort should be made to ensure that subjects are able to provide a 12-hour fasting sample, but samples are to be collected at each scheduled visit as indicated, regardless of the fasting-state of the subject: a. Extended Lipid Panel;
   b. Extended Safety Panel;
   c. Plasma for hs-CRP analysis.
   d. Blood for cardiovascular biomarker analyses – up to 10 mL of plasma and 10 mL of serum for measurement of cardiovascular biomarkers of risk. The 10 mL sample of plasma will be divided into three aliquots of equal volume; the first aliquot is to be distributed to Duke Clinical Research Institute (DCRI), the second aliquot to TIMI, and the third aliquot to the Sponsor. Similarly, the 10 mL sample of serum will be divided into three aliquots of equal volume; the first aliquot is to be distributed to Duke Clinical Research Institute (DCRI), the second aliquot to TIMI, and the third aliquot to the sponsor.
3. Perform urine pregnancy test (all female subjects of childbearing potential).
4. Record adverse events (including concomitant illnesses) and concomitant medications. Record any clinical procedures associated with adverse events. Include questioning for the occurrence of unexplained muscle symptoms.
5. Perform pharmacoeconomic assessment and quality of life assessment (**Appendix 3**).
6. Interview the subject regarding medication compliance and inventory the drug returned by the subject to confirm subject's reported compliance. The assessment may be performed by a qualified health professional designated by the investigator.

7.5.9 Visit at Which Assigned Treatment is Discontinued Early

1. Perform a clinic visit assessment consisting of measurements of blood pressure, pulse, body weight, directed physical examination, and waist circumference. The assessment may be performed by a qualified health professional designated by the investigator.

2. Obtain blood samples for the following laboratory evaluations, performed in place of the Abbreviated Lipid Panel and Abbreviated Safety Panel. The samples may be collected by a qualified health professional designated by the investigator. Every effort should be made to ensure that subjects are able to provide a 12-hour fasting sample, but samples are to be collected at each scheduled visit as indicated, regardless of the fasting-state of the subject: a. Extended Lipid Panel;
   b. Extended Safety Panel;
   c. Pregnancy test (all female subjects of childbearing potential);
3. Record adverse events (including concomitant illnesses) and concomitant medications. Record any clinical procedures associated with adverse events. Include questioning for the occurrence of unexplained muscle symptoms.
4. Perform pharmacoeconomic assessment and quality of life assessment (**Appendix 3**).
5. Interview the subject regarding medication compliance and inventory the drug returned by the subject to confirm subject's reported compliance. The assessment may be performed by a qualified health professional designated by the investigator.

7.5.10 Activities and Assessments to Perform Through the End of the Trial, After a Subject Has Discontinued Assigned treatment Early

1. Record Adverse Events of Special Interest (AESI) as defined in **Section 7.7.2.2.11**.
2. Record concomitant medications.

7.6 Study Procedures

7.6.1 Study Evaluations

The Study Flow Chart in **Section 2.2** summarizes the study procedures to be performed at each visit. Individual study procedures are described below. For details of the procedures for assessment and reporting of adverse events, **Section 7.7.2.2**, Assessment and Reporting of Adverse Events.

In order to minimize variability of evaluations, it is preferred that the same individuals perform the same types of evaluations for all subjects at each study site.

- **Explain Study and Obtain Written Informed Consent:** Screening/ Randomization Visit.

  The investigator or qualified designee will explain the study to the subject, answer all of his/her questions, and obtain written informed consent before performing any study-related procedure. A copy of the informed consent will be given to the subject.

- **Medical History:** Screening/Randomization Visit.

  A medical history will be obtained by the investigator or qualified designee.
  Subject history should include information on family history and personal history. Family history of hypercholesterolemia and/or CHD, alcohol intake, smoking, as well as other coronary risk factors such as

diabetes, hypertension, and obesity should be obtained. Previous and current medications and therapies will be recorded.

- **Review Inclusion/Exclusion Criteria Including Concomitant Medications:** Screening/Randomization Visit.

  The inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that the subject qualifies for the study. Review of all appropriate medication washout times will be discussed with the subject. Cardiovascular-related medications used during the 6 weeks prior to Screening/Randomization will be recorded on the eCRF.

- **Record Adverse Events and Concomitant Medications:** Month 1 and each visit thereafter.

  See **Section 7.7.2.2**, Assessment and Reporting of Adverse Events, and **Section 7.4.2**, Nonstudy Treatments. Cardiovascular-related medication taken chronically by the subject at the time of the initial ACS event prompting hospitalization and before starting the study and cardiovascular-related concomitant therapy taken by the subject during the study are to be recorded on the eCRF. During the trial, concomitant medication prescribed in response to an SAE are to be recorded on the eCRF. The use of any concomitant medication must relate to an adverse event or the subject's medical history.

- **Clinic Visit Assessment:** Each visit.

  This will include measurements of blood pressure and pulse after the subject has remained seated for at least 5 minutes, measurement of body weight without shoes and heavy clothing, and measurement of height without shoes. Height is measured only at the Screening/Randomization Visit.

- **Directed Physical Examination:** Screening/Randomization Visit, Annually, and at Study Completion or early discontinuation of study treatment.

  This will include examination of the skin, head, neck, pulses, lungs, heart, abdomen, extremities, and neurologic system. Abnormal findings not present at baseline will be considered adverse events and recorded as such in the source documentation and transcribed to the eCRF. If the subject is discontinued from study medication for any reason during the treatment phase, every attempt should be made to perform a final physical examination.

- **Pharmacoeconomic Assessment:** Month 1 Visit and each visit thereafter, including Completion or early discontinuation of study treatment.

  This will include collection of data regarding procedures and therapies, length of stay in the Intensive Care Unit (ICU) or Cardiac Care Unit (CCU), major medical complications (see **Appendix 3** for details).

- **Health Utility Assessment:** Each visit, including Completion or early discontinuation of study treatment.

7.6.2 Laboratory Testing

All laboratory tests will be routed to the central laboratory. Subjects will be asked to fast for 12 hours prior to any laboratory tests. Every effort should be made to ensure that subjects are able to provide a 12-hour fasting sample, but samples are to be collected at each scheduled visit as indicated, regardless of the fasting-state of the subject. See **Table 4** for a summary of the laboratory tests.

- **Abbreviated Safety Panel:** Month 1 Visit, Month 4 Visit, 8 Month Visit, 16 month

Visit.
Abbreviated Safety Panel will require approximately 7.5 mL of blood. The Abbreviated Safety Panel should be repeated as required during the entire study. Abbreviated Safety Panel includes assessments of ALT, AST, ***and CPK*** activities. The Abbreviated Safety Panel is delineated in **Appendix 2**.

- **Extended Safety Panels:** Screening/Randomization Visit, Annually, and at Study Completion or early discontinuation of study treatment.

  Approximately 9.5 mL of blood will be required for each Extended Safety Panel. The Extended Safety Panel should be repeated as required during the entire study. Extended Safety Panel includes all of the Abbreviated Safety Panel plus Chemistry (includes total protein, albumin, calcium, inorganic phosphorous, glucose (preferred fasting), blood urea nitrogen [BUN], uric acid, total bilirubin, alkaline phosphatase, serum creatinine, Na, K, Cl, GGT, LDH, Bicarbonate) and complete blood count (CBC) (includes differential, white blood cells [WBC], platelet count, hemoglobin, hematocrit). The Extended Safety Panel is delineated in **Appendix 2**.

- **Abbreviated Lipid Panel:** Month 1 Visit, Month 4 Visit, 8 Month Visit, 16 month Visit.
  Abbreviated Lipid Panel will require approximately 2.5 mL of blood. The Abbreviated Lipid Panel consists of LDL-C using the Friedewald calculation, total cholesterol (TC), HDL-C, and triglyceride (TG) determination. If TG are >400 mg/dL (>4.5 mmol/L), the central laboratory will perform beta-quantitation (direct) measurement of LDL-C and HDL-C. Lipid measurements are delineated in **Appendix 2**.

- **Extended Lipid Panel:** Screening/Randomization Visit, Annually, and at Study Completion or early discontinuation of study treatment.

  Approximately 2.5 mL of blood will be required for each Extended Lipid Panel. The Extended Lipid Panel consists of all of the Abbreviated Lipid Panel, apolipoprotein A-1 (Apo A-1), apolipoprotein B (Apo B), and lipoprotein (a) (Lp(a)), HDL subfractions (HDL_2-C and HDL_3-C), non-HDL-C, and the ratios (LDL-C:HDL-C and TC:HDL-C) determinations. Lipid measurements are delineated in **Appendix 2**.

- **Pregnancy Test:** Each Visit.
  At Screening/Randomization, the local laboratory must perform serum or urine pregnancy test on female subjects of child-bearing potential to determine eligibility. At each subsequent visit a serum pregnancy test will be performed by the central laboratory on all female subjects of childbearing potential through the Month 16 visit. A urine pregnancy test will be performed at each subsequent visit through the end of participation.

- **Blood for Cardiovascular Biomarker Analyses:** Screening/ Randomization Visit, Month 1 Visit, Month 4 Visit, Month 8 Visit, Annually, and Study Completion, but not early discontinuation of study treatment nor at the time of a suspected clinical endpoint event.

  Up to 10 mL of plasma and 10 mL of serum will be drawn and transported to the central laboratory (**Section 10.3**) for assessment of cardiovascular biomarkers of risk. The biomarkers may include, but are not limited to, markers of inflammation immune activation (eg, neopterin), endothelial function (eg, E-selectin), coagulation (eg, tissue factor), platelet activation (eg, CD40-ligand), hemodynamic perturbation (eg, brain natriuretic peptide [BNP]), metabolic abnormality (eg, Adiponectin), and cholesterol absorption and synthesis (eg, phytosterols and lathosterol). The 10 mL sample of plasma will be divided into three aliquots of equal volume; the first aliquot is to be distributed to Duke Clinical Research Institute (DCRI), the second aliquot to TIMI, and the third aliquot to the sponsor. Similarly, the 10 mL sample of serum will

be divided into three aliquots of equal volume; the first aliquot is to be distributed to Duke Clinical Research Institute (DCRI), the second aliquot to TIMI, and the third aliquot to the sponsor.

- **hs-CRP:** Screening/Randomization Visit, 1 Month Visit, 4 Month Visit, 8 Month Visit, Annually thereafter, and Study Completion, but not early discontinuation of study treatment nor at the time of a suspected clinical endpoint event.

  Approximately 2.5 mL of blood will be drawn for measuring hs-CRP by the central laboratory.

- **Calculated Creatinine Clearance (CrCl) and CPK:** Screening/Randomization Visit:

  Creatinine clearance is to be calculated according to the Cockcroft-Gault equation (**Section 7.3.2**, Criterion 8).

$$(140 - age) * (weight\ in\ kg)$$

a. Men: $CrCl = \frac{(140 - age) * (weight\ in\ kg)}{72 * serum\ creatinine\ in\ mg/dL}$

b. Women: $CrCl = \frac{(140 - age) * (weight\ in\ kg)}{72 * serum\ creatinine\ in\ mg/dL} * 0.85$

Table 4 Laboratory Tests

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Hematology	Chemistry	Urinalysis
RBC	Total protein	(None)
Hematocrit	Albumin	
Hemoglobin	Calcium	
Platelets	Inorganic phosphorus	
WBC	Blood urea nitrogen (BUN)	
Eosinophils	Total Bilirubin	
Neutrophils	Alkaline phosphatase	
Lymphocytes	AST (SGOT)	
Monocytes	ALT (SGPT)	

Basophils	GGT LDH Creatinine Glucose Potassium Sodium Chloride Bicarbonate Cholesterol (Total, LDL-C, and HDL-C) Lipids and Triglycerides Serum pregnancy test (beta hCG) Uric acid ***Creatine Phosphokinase (CPK)***	

7.6.3 *Managing Subjects Receiving Simvastatin 80 mg*

Recent USA labeling changes for simvastatin 80 mg based on findings from large clinical trials and other databases suggest that the risk of serious muscle toxicity with simvastatin 80 mg is greater than that seen with certain newer statins that can produce similar or greater LDL-C lowering. The increased risk is greatest during the first year of treatment. With this amendment #5, no additional subjects will have their simvastatin dose increased to 80 mg. Subjects already receiving simvastatin 80 mg will be managed as follows:

- ***Subjects who have been taking the simvastatin dose of 80 mg for less than 12 months will have their dose decreased to 40 mg. The subjects will be contacted as soon as possible, informed of the changes to the trial, and instructed to stop taking medication from Bottle C.***

- ***Subjects who have been tolerating the simvastatin dose of 80 mg for 12 months or longer without evidence of significant toxicity will continue on the 80 mg dose and do not need to be contacted early (unless they are known to be taking amlodipine or ranolazine concomitantly [Section 7.6.6]).***

To minimize the effect of these simvastatin dose changes on the study blind, a proportion of subjects who had already been recalled as a "dummy titration" subject for testing of LDL-C but did not have his/her simvastatin dose increased to 80 mg will be contacted similarly and instructed to discontinue taking medication from Bottle C. Among all the subjects contacted and instructed to stop taking medication from Bottle C, the ratio of subjects who had been actually receiving simvastatin 80 mg to "dummy titration" subjects will be 2:1.

The process will be managed as follows with assistance from the Sponsor's designee:

- ***Each site will be provided with a list of subjects at that site who need to be contacted;***

- ***The site must contact the subjects on the list and do the following: • Review the changes to simvastatin dosing and answer all questions related to the trial;***

- ***Instruct the subject to stop taking medication from Bottle C;***
- ***Remind the subject to return for the next scheduled visit for providing informed consent. Collecting informed consent may occur sooner at an unscheduled visit if appropriate and feasible;***
- ***The site must record all changes in the subject's records and register in the IVRS.***

Subjects who are not on the site list for contacting will be managed as follows:

- ***The subject will simply return for the next regularly scheduled visit;***
- ***At the next regularly scheduled visit, or sooner if appropriate, the site will review the changes to simvastatin dosing and answer all questions related to the trial. The subject must provide written informed consent to continue in the trial;***
- ***If the subject decides to avoid the possibility of receiving the simvastatin 80 mg dose, the site will instruct the subject to stop taking medication from Bottle C;***
- ***The site must record all changes in the subject's records and register in the IVRS.***

All subjects who stop taking medication from Bottle C will have their LDL-C measured for the trial no later than the next schedule visit. If deemed medically appropriate by the investigator, subjects who stop Bottle C should return to the clinic earlier for an LDL-C assessment.

7.6.4 Procedure for Early Discontinuation (Safety Stopping Rules)

7.6.4.1 Elevation in Liver Function Test

At any time during the study, should there be an increase in a subject's ALT and/or AST levels 3 x ULN believed to be related to study drug, the following actions will be implemented according to the situation:

1. If a subject is found to have an ALT and/or AST measurement 3 x ULN, then the subject is to return in approximately 1 week to repeat the blood work.
2. If the same transaminase activity is 3 x ULN on two consecutive occasions (ie, an observation of elevated transaminase activity at a regularly scheduled visit that is confirmed to be elevated upon repeat measurement), the study medication will be interrupted.
3. The subject's laboratory tests will be repeated approximately every 2 weeks until the transaminase activity decreases to <2 x ULN, at which time study drug may be restarted at the discretion of the investigator following discussion with the sponsor's clinical monitor. Treatment is to be restarted at the

same double-blind treatment as assigned at randomization; a new treatment kit will be assigned to the subject.

4. A subject who goes on to have a second episode of two consecutive observations of transaminase activity ≥3 x ULN believed to be related to study drug is to be discontinued from study medication, but will be monitored for any endpoint event until the termination of the study. The subject's laboratory tests will be repeated until resolution at the investigator's discretion with a minimum of weekly testing.

If the liver function test criterion necessitating study medication discontinuation is met, this constitutes an adverse event of special interest (AESI) and must be reported to the sponsor as soon as possible (**Section 7.7.2.2.11**). If the ALT and/or AST elevation meets the criteria for an SAE (**Section 7.7.2.2.5**), it will be reported as such, also.

7.6.4.2 Elevation in Creatine Phosphokinase (CPK) Levels, Definition of Myopathy, Rhabdomyolysis, and Renal Injury

All subjects enrolling in the study will be advised to report promptly any unexplained or unusual muscle symptoms (eg, pain, tenderness, or weakness) to the investigator, which will prompt the measurement of a serum CPK concentration. Serum CPK will be routinely measured at baseline ***and each regularly scheduled visit*** (***see Study Flow Chart)*** in all subjects. ***CPK measurement is included in the routine Abbreviated and Extended Safety Panels performed at specified visits (effective 28 SEP 2010, as described in Memo 217 to Principal Investigators and Research Coordinators).***

At any time during the study, should there be an increase in a subject's CPK level to ≥5 x ULN believed to be related to study drug, the following actions will be implemented according to the situation:

1. CPK ≥10 x ULN with unexplained muscle symptoms consistent with myopathy ***(weakness, pain, soreness not due to new exercise, unusual physical activity, or trauma)***:
   a. Study medication is to be interrupted immediately and CPK is to be measured again as soon as possible.
   b. If the repeat CPK measurement and further clinical evaluation confirm the diagnosis or suspicion of myopathy, study medication is NOT to be resumed.
   c. Study drug may only be resumed if there is no suspicion that the prior CPK elevation reflected drug-related myopathy. In such cases, study drug is to be restarted with the same double-blind treatment as assigned at randomization ***with appropriate CPK monitoring***.
2. CPK ≥5 x ULN with no clinical signs of myopathy:
   a. The subject is to be instructed to refrain from activities that may have contributed to the elevated CPK and CPK is to be measured again as soon as possible. The subject may continue to receive study medication.
   b. If the repeat CPK measurement confirms the observation of elevated CPK levels ***≥5 x ULN***, the subject will have the blood work repeated weekly and may continue to receive study medication, ***provided the suspicion of statinrelated myopathy is low. If the CPK level is >10xULN***

after one to two weeks, however, study medication should be discontinued. The subject should have blood work repeated weekly until the event resolves.

c. If the CPK value decreases to <2 x ULN, blood work ***may*** be resumed on its regular schedule.

3. CPK ≥5 x ULN and <10 x ULN with unexplained or unusual symptoms consistent with myopathy in the absence of muscle trauma:

   a. The subject is to be instructed to refrain from activities that may have contributed to the elevated CPK and CPK is to be measured again as soon as possible. The subject may continue to receive study medication after the first observation of elevated CPK, although the investigator should interrupt treatment, if clinically warranted ***(eg, if symptoms progress or persist or there is otherwise strong suspicion of statin-related myopathy)***.

   b. If the repeat CPK measurement confirms the observation of elevated CPK levels and further clinical evaluation confirm the diagnosis or suspicion of myopathy, study medication is to be discontinued immediately. The subject will have the blood work repeated weekly until the event resolves.

Note: As stated above, subjects with asymptomatic mild elevations in CPK may continue study drug, but with close monitoring and early, repeat measurement of CPK. However, if the CPK remains elevated (>10xULN regardless of symptoms or ≥5 x ULN and <10 x ULN with persistent unexplained symptoms, renal dysfunction, or liver function abnormalities such as an ALT elevation to >1.5xULN), study drug should be stopped. If a subject is reported as having myopathy, rhabdomyolysis, or if the CPK criterion necessitating study medication discontinuation is met, this constitutes an AESI. AESIs will be recorded in the database, monitored by the DSMB, and evaluated and reported in the clinical study report.

Myopathy is defined by either of the following criteria:

1. Otherwise unexplained muscle pain, weakness, or tenderness with CPK ≥10 x ULN; or
2. Otherwise unexplained muscle pain, weakness, or tenderness with two consecutive observations of CPK ≥5 x ULN and <10 x ULN.

At any time during the study, if a subject should present with symptoms consistent with rhabdomyolysis, study medication is to be discontinued immediately.

Rhabdomyolysis is defined by either of the following criteria:

1. Otherwise unexplained muscle pain, weakness, or tenderness and CPK ≥10,000 mU/mL; or
2. Otherwise unexplained muscle pain, weakness, or tenderness with CPK ≥10 x ULN with evidence of renal injury.

Renal injury is defined by at least one of the following three criteria:

1. Increased creatinine levels (absolute increase of □0.5 mg/dL or a relative increase of □50% compared with the last available creatinine level preceding the event); 2. Myoglobinuria; or

3. Brown urine.

If the CPK criterion necessitating study medication discontinuation is met, this constitutes an AESI and must be reported to the sponsor as soon as possible (**Section 7.7.2.2.11**). If the CPK elevation meets the criteria for an SAE (**Section 7.7.2.2.5**), it will be reported as such, also.

7.6.5 Monitoring Subjects Who Are Discontinued From Study Medication Prior to Completion

Subjects who are discontinued from study medication according to the criteria in **Section 7.3.3** prior to completion will be monitored for adverse events, including serious adverse events that start 30 days or fewer after terminating study medication. Subjects who discontinue study medication early will be followed beyond 30 days to the conclusion of the whole trial via telephone contact according to the specified visit schedule; these subjects will be followed for the occurrence of primary clinical endpoint events, administration of any lipid-lowering treatments, and occurrences of Adverse Events of Special Interest (AESI) which are defined in **Section 7.7.2.2.11**. Subjects who are discontinued from study medication will be asked to return for an end-of-study assessment as described in **Section 7.5.9**.

All clinical endpoint events reported for subjects who are discontinued from study medication will be adjudicated by the Clinical Endpoints Committee (CEC) just like all other clinical endpoint events.
A subject that reaches a non-fatal clinical endpoint (**Table 5**) should continue to receive blinded study medication to the end of the trial. The occurrence of a non-fatal clinical endpoint is not a reason for discontinuing study medication.

7.6.6 *Managing Concomitant Use of Study Medication and Amlodipine or Ranolazine*

With this amendment #5, subjects who must receive the dihydropyridine amlodipine or the medication ranolazine concomitant with study medication will have their simvastatin dose limited to a maximum of 40 mg, regardless of whether the subjects were tolerating the simvastatin 80 mg dose for 12 months or longer. Subjects receiving amlodipine or ranolazine with study medication that includes simvastatin 80 mg will need to either reduce the simvastatin dose to 40 mg or stop taking the prescribed amlodipine or ranolazine. The potential use of alternative medications to amlodipine or ranolazine must be coordinated with the subjects' physician. The reduction of the simvastatin dose in subjects who are unable to switch to an alternative to amlodipine or ranolazine will be managed as follows:

- ***With assistance from the Sponsor's designee the site must identify subjects receiving a simvastatin dose of 80 mg plus amlodipine or ranolazine as follows:***

- ***Each site will be provided with a list of all subjects at that site who are receiving study medication that includes a simvastatin dose of 80 mg and a dihydropyridine (Note that this***

list will include any dihydropyridine because specific dihydropyridines are not being recorded in the trial database. However, the dosing restriction with amlodipine and simvastatin does not apply to other allowed agents in this class such as nifedipine, felodipine, and nicardipine). The list will also include some "dummy titration" subjects. The ratio of subjects receiving simvastatin 80 mg to dummy titration subjects will be 2:1. The site will review the local documentation for the subjects on the list and identify those subjects who are actually receiving the amlodipine;

- ***The site will review the local documentation of all subjects at that site and identify those subjects who are receiving ranolazine concomitantly to study medication.***

- ***The site must contact each subject identified and inform them of the need to either stop taking amlodipine or ranolazine or stop taking medication from Bottle C. The option of stopping amlodipine or ranolazine with the possible substitution of alternative medications or modification of other medications must be carefully coordinated with the subject's physician, including appropriate follow-up after a potential change;***

- ***At the next regularly scheduled visit or sooner if appropriate, the site will review the changes to simvastatin dosing and answer all questions related to the trial. The subject must provide written informed consent to continue in the trial;***

- ***The site will reinforce to any subject receiving study medication and concomitant amlodipine or ranolazine of the need to avoid all other prohibited drugs and report promptly any unexplained muscle symptoms which will trigger laboratory assessment of CPK;***

- ***The site must record all changes in the subject's records and register in the IVRS.***

All subjects who stop taking medication from Bottle C will have their LDL-C measured for the trial no later than the next schedule visit. If deemed medically appropriate by the investigator, subjects who stop Bottle C should return to the clinic earlier for an LDL-C assessment.

7.7 Study Assessments

7.7.1 Efficacy

7.7.1.1 Endpoints

The clinical endpoint events are summarized in **Table 5**. Clinical endpoint events will be specifically defined by the CEC Charter (**Section 9.3.2**).

Table 5 Components of Composite Clinical Coronary Endpoint Events and Individual Clinical Endpoint Events

Protocol No. P04103

Primary Endpoint Events and Primary Composite Endpoint	Secondary Composite Endpoint (a)	Secondary Composite Endpoint (b)	Secondary Composite Endpoint (c)	Tertiary Individual Endpoints

CV Death, Major Coronary Events, and Stroke	All Death, Major Coronary Events, and Stroke	CHD Death, Non-fatal MI, and Urgent Coronary Revascularization	CV Death, Vascular Events, and Stroke	All Individual Endpoints[a]
CV Death			CV death	CV death
	Death from any cause			Death from any cause
		CHD death		CHD death
Non-fatal MI[b]	Non-fatal MI[b]	Non-fatal MI[b]	Non-fatal MI[b]	
				MI[b]
Documented unstable angina requiring hospitalization	Documented unstable angina requiring		Documented unstable angina requiring	Documented unstable angina requiring

Table 5 Components of Composite Clinical Coronary Endpoint Events and Individual Clinical Endpoint Events

Protocol No. P04103

Primary Endpoint Events and Primary Composite Endpoint	Secondary Composite Endpoint (a)	Secondary Composite Endpoint (b)	Secondary Composite Endpoint (c)	Tertiary Individual Endpoints
CV Death, Major Coronary Events, and Stroke	All Death, Major Coronary Events, and Stroke	CHD Death, Non-fatal MI, and Urgent Coronary Revascularization	CV Death, Vascular Events, and Stroke	All Individual Endpoints[a]
	hospitalization		hospitalization	hospitalization
All coronary revascularization with PCI or CABG[c]	All coronary revascularization with PCI or CABG[c]			All coronary revascularization with PCI or CABG[c]
		Urgent coronary revascularization with PCI or CABG[c]		Urgent coronary revascularization with PCI or CABG[c]
			All revascularization[c,d]	All revascularization[c,d]
Non-fatal Stroke[b]	Non-fatal Stroke[b]		Non-fatal Stroke[b]	
				Stroke[b]
				Any CV event leading to hospitalization

				CHF that requires hospitalization[e]
				Dual Goal for LDL-C/hs-CRP[f]

CABG = Coronary Artery Bypass Grafting; CHD = Coronary Heart Disease; CHF = Congestive Heart Failure; CV = Cardiovascular; MI = Myocardial Infarction; PCI = Percutaneous Coronary Intervention

[a] All individual endpoints are to be analyzed as a tertiary objective.

[b] All MIs and all strokes are to be analyzed individually. However, because each composite endpoint already captures deaths caused by MI or stroke, only non-fatal MIs and non-fatal strokes are components of the composite endpoints.

[c] Revascularization must occur at least 30 days after randomization to be included as a clinical endpoint event in the analyses.

[d] "All revascularization" includes coronary revascularization and non-coronary revascularization.

[e] CHF that requires hospitalization must occur at least 30 days after randomization to be considered a clinical endpoint event.

[f] Percentage of subjects achieving concentrations of LDL-C <70 mg/dL(<1.8 mmol/L) in addition to hs-CRP <2.0 mg/L following 1 month and 4 months of treatment with Ezetimibe/Simvastatin Combination or simvastatin.

7.7.1.1.1 Primary Endpoint

The primary efficacy endpoint measure will be the time from randomization until the first occurrence of one of the following: CV death, major coronary events (non-fatal MI, documented unstable angina that requires admission into a hospital, all coronary revascularization with either PCI or CABG occurring at least 30 days after randomization), or non-fatal stroke.

7.7.1.1.2 Secondary Endpoint

The secondary efficacy endpoint measures will be as follows:

1. Time from randomization until the first occurrence of death due to any cause, major coronary events, or non-fatal stroke.
2. Time from randomization until the first occurrence of CHD death, non-fatal MI, or urgent coronary revascularization with either PCI or CABG occurring at least 30 days after randomization.
3. Time from randomization until the first occurrence of CV death, non-fatal MI, documented unstable angina that requires admission into a hospital, all revascularization ("All revascularization" includes coronary revascularization and non-coronary revascularization) occurring at least 30 days after randomization, and non-fatal stroke.

7.7.1.1.3 Tertiary Efficacy Endpoints The tertiary endpoint

measures will be as follows:

1. Individual Endpoints:

   The individual tertiary outcomes measures will be the time from randomization until the first occurrence for each of the following individual events: death from any cause, CHD death, CV death, MI, documented unstable angina that requires admission into a hospital, all coronary revascularization with either PCI or CABG occurring at least 30 days after randomization, urgent coronary revascularization with either PCI or CABG occurring at least 30 days after randomization, all revascularization (including both coronary and non-coronary) occurring at least 30 days after randomization, stroke, any cardiovascular event leading to admission into a hospital, CHF that requires hospitalization occurring at least 30 days after randomization.

2. Reductions in LDL-C and hs-CRP:

   The LDL-C/hs-CRP endpoint will be the percentage of subjects achieving concentrations of LDL-C <70 mg/dL (<1.8 mmol/L) in addition to hs-CRP
   <2.0 mg/L following 1 month and 4 months of treatment with Ezetimibe/Simvastatin Combination or simvastatin

7.7.1.2 Appropriateness of Measurements

The study design is appropriate for the indication studied. Validated methods of data collection, analysis, and evaluation will be used for the study.

7.7.2 Safety

7.7.2.1 Specification of Safety Variables

Safety variables to be assessed include safety laboratory tests (including liver function tests and CPK levels), physical examinations, assessment of adverse events, and clinic assessments.

7.7.2.2 Assessment and Reporting of Adverse Events

An adverse event (AE) is any untoward medical occurrence in a subject administered a pharmaceutical product, biologic (at any dose), or medical device, which does not necessarily have a causal relationship with the treatment. AEs may include the onset of new illness and the exacerbation of pre-existing conditions.

All AEs must be recorded in the subject's medical records and on the eCRF. The onset and end dates, severity and relationship to study drug will be recorded for each AE. The severity of the AE will be assessed according to specific guidelines (**Section 7.7.2.2.1**). Any action or outcome (eg, hospitalization, discontinuation of therapy, etc) will also be recorded for each AE.

Subjects will be questioned and/or examined by the investigator or a qualified designee for evidence of AEs. The questioning of subjects with regard to the possible occurrence of adverse events will be generalized such as, "How have you been feeling since your last visit?" although subjects will be questioned for the occurrence of unexplained muscle symptoms at all clinic visits.

7.7.2.2.1 Assessment of Adverse Event Severity and Relationship to Treatment

Where the determination of adverse event severity rests on medical judgment, the determination of severity must be made with the appropriate involvement of a medically-qualified investigator.

The severity of AEs will be graded using the following definitions:

Mild: awareness of sign, symptom, or event, but easily tolerated;

Moderate: discomfort enough to cause interference with usual activity and may warrant intervention;

Severe: incapacitating with inability to do usual activities or significantly affects clinical status, and warrants intervention;

Life-Threatening: immediate risk of death.

A medically-qualified investigator must assess the relationship of any AE to the use of study drug, based on available information, using the following guidelines:

Unlikely related: no temporal association, or the cause of the event has been identified, or the drug, biological, or device cannot be implicated;

Possibly related: temporal association, but other etiologies are likely to be the cause; however, involvement of the drug, biological, or device cannot be excluded;

Probably related: temporal association, other etiologies are possible, but unlikely.

The expectedness of an adverse reaction shall be determined according to the reference document. The reference document for this current study is to be the local label.

7.7.2.2.2 Monitoring Adverse Events

Subjects having AEs will be monitored with relevant clinical assessments and laboratory tests, as determined by the investigator. The investigator or qualified designee is expected to report ongoing AEs at completion of the clinical study to the primary care physician who will determine the need for and provide standard medical care.

Any actions taken and follow-up results must be recorded either on the appropriate page of the eCRF or in a follow-up letter to the sponsor, as well as in the subject's source documentation. Follow-up laboratory results should be filed with the subject's source documentation.

For all AEs that require the subject to be discontinued from the study, relevant clinical assessments and laboratory tests will be repeated as clinically appropriate, until final resolution or stabilization of the event(s).

7.7.2.2.3 Known Adverse Events Relating to the Underlying Clinical Condition

Known complications relating to high-risk ACS are designated as clinical endpoint events (**Section 7.7.1.1**).

7.7.2.2.4 Known Potential Toxicities of Study Drug

The AEs mentioned under this section still need to be recorded in the subject's medical records and on the eCRF regardless of causality.

7.7.2.2.4.1 Ezetimibe/Simvastatin Combination

Refer to the Investigator's Brochure and the most recent local package insert for Ezetimibe/Simvastatin Combination, specific to each country, for additional information on observed AEs.

7.7.2.2.4.2 Simvastatin

Refer to the most recent, local Package Insert for ZOCOR (simvastatin), specific to each country, for details of observed AEs.

7.7.2.2.5 Definition of Serious Adverse Events

A serious adverse event (SAE) is any adverse drug or biologic or device experience occurring at any dose that results in any of the following outcomes:

- death;
- life-threatening AE (ie, one that places the subject, in the view of the initial reporter, at immediate risk of death from the AE as it occurs);
- persistent or significant disability/incapacity;

- requires in-patient hospitalization (ie, admission), or prolongs hospitalization;
- congenital anomaly or birth defect.

Additionally, **important medical events** that may not result in death, be lifethreatening, or require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in in-patient hospitalization, or the development of drug dependency or drug abuse.

Any suspected clinical endpoint event that may also be an SAE, is not to be reported in an expedited manner to the sponsor's Drug Safety Surveillance department.
However, each suspected clinical endpoint event will be monitored by the Data Safety Monitoring Board (DSMB, **Section 9.3.1**) to ensure subject safety (**Section 7.7.2.2.10**).

Unless exempted as described in Section 7.7.2.2.10, **all SAEs**, whether or not deemed drug-related or expected, **must be reported** by the investigator or qualified designee to the sponsor's Drug Safety Surveillance [DSS] department **within 1 working day of first becoming aware of the event**. If the report is given to the sponsor via telephone rather than in writing on the form designated for SAE reporting, a full description of the event and any sequelae, including the investigatordetermined causality to study drug must be provided, so that the appropriate written report can be completed by the designated sponsor contact. SAEs that occur at any time after the inclusion of the subject in the study up to 30 days after the subject completed or discontinued the study medication (**Section 7.2.2**) must be reported. In the specific circumstance of screen failures, SAEs must be collected from the time of consent signing until the subject is considered a screen failure.

Reports of all **SAEs** must be communicated as soon as possible to the appropriate Institutional Review Board (IRB) or Independent Ethics Committee (IEC) and/or reported in accordance with local laws and regulations.

7.7.2.2.6 Reporting of Subject Death

Because death from any cause is a clinical endpoint event, the death of a subject occurring after enrollment or prior to the end of monitoring is not to be reported to the sponsor's Drug Safety Surveillance department. Death is to be recorded in the eCRF in the clinical endpoints events module and will be monitored by the DSMB to ensure subject safety (**Section 7.7.2.2.10**).

If an autopsy is performed, the report must be provided to the sponsor.

Reports of all deaths, must be communicated as soon as possible to the appropriate IRB or IEC and/or reported in accordance with local law and regulations.

7.7.2.2.7 Reporting of Pregnancies

Pregnancy information on clinical study subjects is collected by the sponsor's Drug Safety Surveillance department. If a subject should become pregnant during the course of the study, the investigator or qualified designee must contact the sponsor's DSS department within 5 working days of the investigator or qualified designee first becoming aware of the pregnancy. If a serious adverse event occurs in conjunction with the pregnancy, the SAE **must be reported** by the investigator or qualified designee to the sponsor's Drug Safety Surveillance [DSS] department **within 1 working day of first becoming aware of the event**. The sponsor's representative will provide instructions on how to collect pregnancy information. Follow-up information on the outcome of the pregnancy should also be forwarded to the sponsor.

7.7.2.2.8 Preplanned Hospitalizations or Procedures

During the study, if a subject has a hospitalization or procedure (eg, elective surgery) that was scheduled prior to the subject entering the study (ie, before the subject signed the informed consent) for an event/condition that occurred before the study, the hospitalization is considered a therapeutic intervention and not the result of an SAE. However, if the event/condition worsens during the study, it must be reported as an AE (or SAE, if the event/condition results in a serious outcome such as hospitalization).

7.7.2.2.9 Reports of Overdose

An overdose of Ezetimibe/Simvastatin Combination is any dose higher than that given in approved labeling. Similarly, an overdose of simvastatin is any dose higher than that provided in the Reports of Overdose section of the approved labeling.

For this current IMPROVE-IT trial, an overdose of ezetimibe is defined as □40 mg in a 24 hour period; an overdose of simvastatin is defined as □160 mg in a 24 hour period. Thus, to accommodate the packaging and maintain the blinding of study treatment, a overdose is defined as 4 or more tablets ingested from any single study bottle dispensed during the course of the study in a 24 hour time period.

Information on overdoses in clinical subjects is collected by the sponsor's Drug Safety Surveillance department. Should a subject experience an overdose during the course of the study (whether symptomatic or not), the investigator or qualified designee must contact the sponsor's DSS department, within 5 working days of the investigator or qualified designee first becoming aware of the overdose. Follow-up information on the outcome of the overdose should be forwarded to the sponsor.

Any event associated with, or observed in conjunction with, a product overdose (whether accidental or intentional) or a product abuse and/or withdrawal is considered an AE and should be reported as such (**Section 7.7.2.2**). If a serious adverse event occurs in conjunction with the overdose, then the reporting time frame for an SAE (1 working day) must be met. The sponsor's representative will provide instructions on how to collect this information.

7.7.2.2.10 Protocol-Specific Exceptions to SAE Reporting to Drug Safety Surveillance

In this trial each suspected clinical endpoint event is to be reported in the clinical endpoint events module of the eCRF. The CEC will adjudicate each suspected clinical endpoint event according to its guidelines stated in the CEC Manual of Operations (**Section 9.3.2**). The DSMB will monitor safety data and suspected clinical endpoint events to ensure subject safety. A suspected clinical endpoint event, regardless of when the event occurs, is not to be reported as an AE or SAE in the eCRF or reported in an expedited manner to the sponsor's Drug Safety Surveillance (DSS) department as an SAE (**Section 7.7.2.2.5**).

The suspected clinical endpoint events are listed below:

Death from any cause, MI, unstable angina, all revascularization (including both coronary and non-coronary), stroke, any CV event leading to hospitalization, and CHF.

7.7.2.2.11 Reporting Adverse Events of Special Interest

The events listed below are to be reported as Adverse Events of Special Interests (AESI) because of their association with lipid-lowering treatments. These AESIs are not collected for the endpoint analyses, but as a safety measure. All AESI, whether or not deemed drug-related, serious, or expected, are to be captured in the AE Module of the eCRF. They are not to be reported to the sponsor in an urgent manner. AESIs will be recorded in the database, monitored by the DSMB, and evaluated and reported in the clinical study report.

1. Defined increases in AST, ALT (**Section 7.6.4.1**);
2. Defined increases in CPK (**Section 7.6.4.2**);
3. All AEs reflective of gallbladder-disease;
4. All cholecystectomies;
5. All occurrences of myopathy and rhabdomyolysis (**Section 7.6.4.2**).

7.7.2.3 Reporting of Investigational Medicinal Product Quality Complaints

Any defect or possible defect in an investigational medicinal product (defined as a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial) must be reported by the investigator or qualified designee to the sponsor's study monitor **within 1 working day** of first becoming aware of the possible defect. This report to the sponsor may be made by telephone or by faxing the Investigational Medicinal Product Quality Complaint (IMPQC) form to the designated sponsor representative. The product and packaging components in question, if available, must be stored in a secure area under specified storage conditions until it is determined whether the product is required to be returned for investigation of the defect. If the product complaint is associated with an SAE, the SAE must be reported separately in accordance with the protocol, and the SAE report should mention the product quality complaint.

7.7.3 Pharmacogenomics

Participation in the pharmacogenomics analyses is optional. Subjects who do not consent for this DNA collection may still participate in the IMPROVE-IT Study.

7.7.3.1 Description

DNA will be collected from willing subjects and transported to a responsible party performing analyses of the determinants of genes contributing to ACS, any clinical endpoint events, lipid metabolism, subject response to the study treatments and/or genetic polymorphism affecting these genes. Subjects will be requested to sign a separate consent form at the Screening/Randomization Visit to allow for the collection of a whole blood sample from which DNA will be extracted. The sample for possible pharmacogenomic analysis will be collected only if subject, health authorities, ethics committee and study center are in agreement. Subjects who do not consent for this DNA collection may still participate in the study. Potential analyses may include correlation between genes contributing to atherosclerosis or lipid metabolism and study results/clinical response using pooled anonymous data. Only pooled data sets that are anonymous with regard to subject identification will be analyzed. Collected specimens will remain fully blinded to the study sponsor using an encryption procedure as described in **Section 7.7.3.2**. The encrypted, anonymized specimens may be analyzed by the genetics laboratories of the sponsor or at other laboratories.

7.7.3.2 Confidential Subject Information

Redacted
Redacted

7.7.3.3 Withdrawal From Pharmacogenomic Database

Subjects may withdraw their consent to store the blood sample or the DNA derived from it, without affecting their participation in the IMPROVE-IT Study. The specimens will be destroyed up until the time when the samples have been rendered de-identified. After this point, samples of individual subjects will not be identifiable. Additionally, data derived from genetic analysis of these specimens will have been rendered anonymous after this point and it will be impossible to identify the subject to delete the data.

7.7.3.4 Retention of Data

It is anticipated that data from this study will be retained for an indefinite period. DNA specimens will be analyzed within 20 years from the date of collection and then destroyed in a manner documented and prescribed by the storage facility.

7.7.3.5 Data Security

Pharmacogenomic and other research databases are accessible only to authorized sponsor research personnel and/or designated collaborators and are only stored and accessible as anonymized data. User authentication is accomplished using state-ofthe-art network security technology to protect against unauthorized access. These data are collected for pharmacogenomic research purposes only and will not be used for any other purpose without explicit consent from the research subject.

7.7.4 Criteria for Termination of the Study

The DSMB (**Section 9.3.1**) will retain responsibility for early termination of the study. The criteria that the DSMB will follow to determine when to terminate the study will be described in the DSMB Charter.

8.0 STATISTICAL AND ANALYTICAL PLANS

This is a multi-center, randomized, double-blind, parallel-group study to evaluate the clinical benefit of Ezetimibe/Simvastatin Combination compared with simvastatin in stabilized ACS subjects. ***Approximately*** 18,000 subjects are expected to receive randomized treatment assignment to Ezetimibe/Simvastatin Combination 10/40 or simvastatin 40 mg.

8.1 Data Sets

The intent-to-treat (ITT) population includes all subjects who receive randomized treatment assignment. Specifically, all subjects who receive randomized treatment assignment but never take study drug will be analyzed using the assigned treatment. All other subjects will be analyzed using the actual treatment that they received.
Subjects with protocol deviations or violations will be analyzed in the ITT population.

All the safety and efficacy data will be analyzed based on the ITT population.
Subjects who have their simvastatin dose increased to 80 mg as described in **Section 7.4.1.1.2** and

Section 7.6.3 will be included in the analyses as follows: ● Ezetimibe/Simvastatin Combination

Treatment Group will include subjects receiving:

- Ezetimibe 10 mg and simvastatin 40 mg as one Ezetimibe/Simvastatin Combination 10/40 tablet and two simvastatin 40 mg placebo tablets; and
- Ezetimibe 10 mg and simvastatin 80 mg as one Ezetimibe/Simvastatin Combination 10/40 tablet, one simvastatin 40 mg tablet, and one simvastatin 40 mg placebo tablet. ● Simvastatin Treatment Group will include subjects receiving:
- Simvastatin 40 mg as one Ezetimibe/Simvastatin Combination 10/40 placebo tablet, one simvastatin 40 mg tablet, and one simvastatin 40 mg placebo tablet;
- Simvastatin 80 mg as one Ezetimibe/Simvastatin Combination 10/40 placebo tablet and two simvastatin 40 mg tablets.

8.2 Demographic and Other Baseline Characteristics

Baseline and demographic characteristics such as sex, race, age, etc will be summarized by treatment group to assess treatment group comparability. No formal statistical analyses of these data are planned.

8.3 Efficacy Analyses

Only clinical endpoint events adjudicated by the Clinical Events Committee (CEC) will be used in the final efficacy analyses (**Section 9.3.2**).

The primary endpoint is the composite of CV death, major coronary events (non-fatal MI, documented unstable angina that requires admission into a hospital, all coronary revascularization events with either PCI or CABG occurring at least 30 days after randomized treatment assignment), and non-fatal stroke. The primary efficacy outcome measure will be the time from randomization until the first occurrence of any event in the primary endpoint. The primary hypothesis is that the administration of Ezetimibe/Simvastatin Combination will be significantly more effective in reducing the incidence of primary endpoint events than simvastatin. A Cox proportionalhazard model with covariates of treatment and stratification factors (early use of eptifibatide, experience with chronic prescription lipid-lowering therapy, and high-risk ACS diagnosis) will be used for the primary analysis. Estimates of hazard ratios and associated 95% confidence intervals comparing Ezetimibe/Simvastatin Combination and simvastatin will be provided with the use of this model. Because revascularizations occurring up to 30 days after randomization will not be included in the pre-specified endpoints, the effect of these events will be assessed by sensitivity analyses on the primary endpoint.

Hazard ratios and 95% confidence intervals for each of the categories determined by age, sex, race, diabetes, and prior statin therapy will be provided for the primary endpoint using the Cox proportional-hazard model specified above.

There are three supportive secondary composite endpoints. The first secondary efficacy outcome measure is the time from randomization until the first occurrence of the composite incidences of death from any cause,

non-fatal MI, documented unstable angina that requires admission into a hospital, all coronary revascularization events with either percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) occurring at least 30 days after randomized treatment assignment, and non-fatal stroke. The second secondary efficacy outcome measure is the time from randomization until the first occurrence of the composite incidences of death from coronary heart disease (CHD), non-fatal MI, and urgent coronary revascularization events with either percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) occurring at least 30 days after randomized treatment assignment. The third secondary efficacy outcome measure is the time from randomization until the first occurrence of the composite incidences of CV death, non-fatal MI, documented unstable angina that requires admission into a hospital, all revascularization (including both coronary and non-coronary) occurring at least 30 days after randomized treatment assignment, and non-fatal stroke.

The hypothesis for each secondary endpoint is that Ezetimibe/Simvastatin Combination compared with simvastatin will reduce the incidence of the composite secondary endpoint. Estimates of hazard ratios and associated 95% confidence intervals between the two treatments will be calculated using the same Cox proportional-hazard model specified above for the analysis of the primary endpoint.

Kaplan-Meier estimates for the time to the primary and each of the secondary endpoints will be plotted.

For the individual tertiary endpoint events, the outcomes measure will be the time from randomization until the first occurrence for each of the following: CV death, death from any cause, CHD death, MI, documented unstable angina that requires admission into a hospital, all revascularization (including both coronary and non-coronary) occurring at least 30 days after randomization, stroke, any CV event leading to hospitalization, and CHF that requires hospitalization occurring at least 30 days after randomization. These endpoints measuring outcomes will be analyzed by the Cox proportional-hazard model specified above. Due to the competing risk problems, the results need to be interpreted cautiously.
The other tertiary endpoint is the percent of subjects achieving the dual goal of LDL-C less than 70 mg/dL (1.8 mmol/L) and hs-CRP less than 2 mg/L following 1 month and 4 months of treatment with Ezetimibe/Simvastatin Combination or simvastatin. There are two tertiary hypotheses associated with subjects achieving the dual goal for LDL-C and hs-CRP. The first hypothesis is that Ezetimibe/Simvastatin Combination will result in a greater percentage of subjects achieving both an LDL-C concentration of <70 mg/dL (<1.8 mmol/L) and hs-CRP concentration of <2.0 mg/L compared with simvastatin. The second tertiary hypothesis is that the group of subjects, regardless of treatment, achieving the dual goal of an LDL-C concentration of <70 mg/dL (<1.8 mmol/L) and an hs-CRP concentration of <2.0 mg/L will reduce the incidence of the primary composite endpoint compared with the group of subjects, regardless of treatment, that do not achieve the dual goal for LDL-C and hs-CRP.

There is a single primary efficacy endpoint (composite of CV death, major coronary events [non-fatal MI, documented unstable angina that requires admission into a hospital, all coronary revascularization events with either PCI or CABG occurring at least 30 days after randomized treatment assignment], and non-fatal stroke) and one primary comparison between Ezetimibe/Simvastatin combination and simvastatin monotherapy. Hence, no adjustment for multiplicity is needed for the primary hypothesis. For the secondary hypotheses, details for multiplicity adjustment will be provided in the Data Analysis Plan.

8.4 Safety

Descriptive statistics will be provided for safety data. No inferential analysis of safety data is planned, except for the following parameters of interest. Point estimates and associated 95% confidence intervals for the differences in incidences between the treatment groups will be provided for myopathy/rhabdomyolysis,

cholecystectomy, and ALT/AST 3 x ULN (consecutive/presumed consecutive as defined in **Section 7.6.4.1**). The number of subjects reporting any adverse events (AE), the occurrence of specific AEs, and discontinuation due to AEs will be tabulated. Laboratory data will be listed and values outside the normal range will be flagged.

8.5 Determination of Sample Size/Power/Level of Significance

Approximately 18,000 subjects will receive randomized treatment assignment to either Ezetimibe/Simvastatin Combination 10/40 or simvastatin 40 mg QD, with up to 9000 subjects per treatment group. Treatment with Ezetimibe/Simvastatin Combination 10/40 is expected to result in an approximate mean absolute reduction of 15 mg/dL (0.39 mmol/L) in LDL-C concentration compared with treatment with simvastatin 40 mg, and this is hypothesized to result in an approximate 9.375% reduction in hazard in the primary endpoint event (incidence of CV death, major coronary events, or non-fatal stroke) at 2 years for Ezetimibe/Simvastatin Combination 10/40 over simvastatin 40 mg.

The sample size will be ***approximately*** 18,000 subjects with the trial continuing until accrual of approximately 5250 primary endpoint events, which will provide power in the range of 90%. This sample size is determined from a statistical model approach based on pooled blinded endpoint rates and evaluates the effects of a reduced treatment effect in the first 6 months, enrollment rate, follow-up duration, lag in event rate reporting, differences in population event rates (STEMI and NSTE) and drop-out on power and total event accumulation during the trial. The goal of sample size modeling is to maintain trial power at approximately 90% while minimizing total trial duration. The final sample size will be determined by the statistical modeling approach when adequate patient experience has been accumulated to result in a stable estimate of the primary endpoint event rate. Full details of the modeling approach will be provided in a separate sample size statistical plan.

The independent LDL-C Monitoring Committee (LMC) will periodically review the achieved LDL-C results and advise the Executive Group within the Operations Committee regarding the congruence of the modeling assumptions and the between-treatment group difference in LDL-C changes. The LMC may advise the Executive Group and Operations Committee to increase the minimal number of primary endpoint events to be collected if the difference in median LDL-C between treatment groups is less than anticipated. This review procedure will ensure that the number of primary efficacy endpoints captured is adequate to answer the main trial question. The LMC will provide advice to the Executive Group and Operations Committee once 15,000 subjects are enrolled and again at 1 year prior to the anticipated end of the trial. Details for the LMC operations and analyses are provided in the LMC charter.

8.6 Interim *Analyses*

An independent Data Safety Monitoring Board (DSMB, **Section 9.3.1**) will review safety data on a regular basis according to the schedule specified in the DSMB charter. An independent Duke Clinical Research Institute (DCRI) statistician will be the only individual with access to the randomization code and results. This independent statistician is not involved in the day-to-day project activities. The DCRI study personnel, Executive Committee (**Section 9.3.4**), Steering Committee (**Section 9.3.5**), and sponsors will remain blinded.

Two interim efficacy ***analyses*** will be performed when approximately 50% ***and 75%*** of the expected total primary events are available. The primary analysis will be based on the adjudicated events using the same COX PH model specified for the primary endpoint. Supportive analyses will be performed based on both adjudicated and un-adjudicated events. The O'Brien-Fleming methodology will be implemented to protect the overall type I error of 0.05 using the software East 3. Specifically, a nominal alpha level of 0.003 will be used for the ***first*** interim analysis ***(50% of events) and a nominal alpha level of 0.0184 will be used for the second interim analysis (75% of events). Overwhelming efficacy for early study termination minimally requires significance for the primary efficacy endpoint at the specified nominal significance levels and a directionally consistent reduction in total mortality.*** For the final analysis, the primary endpoint will be tested at a nominal alpha level of 0.04***38***. Details for the interim analyses are provided in the
DSMB charter.[4]

8.7 Data Analysis Plan

Prior to the ***first*** interim analysis, a detailed Data Analysis Plan will be completed and placed on file. The DAP will contain a comprehensive explanation of the methodology used in the statistical analyses. The DAP will also contain the rules and data handling conventions used to perform the analyses, and the procedure used for accounting for missing data.

9.0 ADHERENCE TO ETHICAL, REGULATORY, AND ADMINISTRATIVE CONSIDERATIONS

The ethical and regulatory requirements that must be observed to comply with Principles of Good Clinical Practice (GCP) for the conduct and monitoring of clinical investigations are presented in this section and **Appendix 1**, General Requirements for Clinical Trials. By signing this protocol, the investigator agrees to adhere to these requirements.

The study must be conducted in accordance with GCP as outlined in the
International Conference on Harmonisation of Technical Requirements for
Registration of Pharmaceuticals for Human Use (ICH) Guidelines, E6 Good Clinical Practice: Consolidated Guidance and other applicable laws and regulations. In addition, the study must be conducted in accordance with: (i) the USA Code of Federal Regulations (CFR) if the study is conducted under a USA IND, regardless of the country involved; (ii) the European Union (EU) Clinical Trial Directive (CTD) and local regulations if the study is conducted in the EU; and (iii) any specific local regulations if the study is conducted elsewhere.

9.1 Ethical Conduct of the Study

9.1.1 Independent Ethics Committee or Institutional Review Board

Prior to initiation of the study at any site, the study, including the protocol and informed consent, must be approved by an appropriate Institutional Review Board (IRB) or Independent Ethics Committee (IEC). The IRB/IEC must be constituted according to applicable regulatory requirements. As appropriate, amendments to the protocol must also be approved by the IRBs/IECs before implementation at the sites. The IRB/IEC approval should be obtained in writing, clearly identifying the study, the documents reviewed (including informed consent), and the date of the review.

In the event that the IRB/IEC requires changes in the protocol, the sponsor shall be advised and must approve the changes prior to implementation. The investigator shall not modify the study described in the protocol once finalized and after approval by the IRB/IEC without the prior written approval of sponsor.

In countries where the investigator submits the study protocol and statement of informed consent to the IRB/IEC, the investigator or qualified designee will forward the approvals to the sponsor.

Individual sites will use local IRBs.

9.1.2 Subject Information and Consent

The details of the protocol must be discussed with each potential subject, and written informed consent must be obtained for all subjects before any study-related procedure is performed. In obtaining informed consent, the information must be provided in language and terms understandable to the subject. The subject, or the subject's legal representative, must give their written consent to participate in the study. The signed and dated consent form itself must be retained by the investigator as part of the trial records. A copy of the signed and dated consent form must be given to the subject. The consent form must include all of the required elements of informed consent in accordance with ICH Guidelines E6 and the USA FDA as set forth in Title 21 CFR, Part 50. In addition, the sponsor specifically requests that the consent form identify it as the sponsor and state that use of the drug is experimental and the side effects of the drug are not completely known. The consent form must be approved by the appropriate IRB/IEC and sponsor before study initiation at a study site. Any subsequent changes to the approved informed consent form must be reviewed and approved by the appropriate IRB/IEC and sponsor before implementation.
In emergency situations where consent of the subject or subject's legally authorized representative is not possible, the informed consent procedures must follow ICH and other applicable regulations to protect the rights, safety, and well-being of the subject.

9.1.3 Protocol-Related Regulatory and Ethical Considerations/Issues None.

9.2 Reporting to Sponsor

Contact with the investigator will be maintained by the sponsor's study monitor who will visit the investigator at the initiation and closure of the study and at periodic intervals during the study to assess the conduct of the study.

A screening log entry will be completed for all subjects who have given informed consent. An eCRF will be completed for all subjects who receive randomized treatment assignment. Subjects are not to be identified on the CRF by name; appropriate codes and subject initials should be used. All screening logs or eCRFs/EDC screens should be completed soon after the evaluation has occurred.

An eCRF/EDC screen or screening log with a minimum of the following information shall be completed for subjects who have given informed consent:

(1) demographics, (2) subject status, (3) reason for screen failure, and (4) serious adverse events. Data are to be collected from the time the informed consent form is signed until the subject is determined to have failed screening.

It is essential that all dates appearing on the sponsor's subject data collection forms for laboratory tests, cultures, etc. be the dates on which the specimens were obtained, or the procedures performed. The investigator will acknowledge in writing that he/she has verified the accuracy of the recorded data.

9.3 Study Committees

9.3.1 Data Safety Monitoring Board

An independent Data Safety Monitoring Board (DSMB) will be created to further protect the rights, safety, and well being of subjects who will be participating in this study by monitoring the progress and results. The DSMB will comprise qualified scientists, who are not investigators in the study and not otherwise directly associated with the sponsor. The DSMB will be described in detail in the DSMB Charter.

The DSMB will monitor safety results, especially SAEs, and clinical endpoint events on a continual basis, and may request an unplanned review of all safety data, with unblinding by the entire DSMB if a safety concern arises. The DSMB will monitor the number of subjects achieving the target LDL-C levels and ensure that subjects are receiving therapy that meets the current guidelines.

The DSMB Charter will include a description of all interim analyses to be performed, including how the interim results will be analyzed and how the interim analyses will affect the overall alpha level of 0.05 for the study.

All activities of the DSMB will be documented. This documentation will include data summaries and analyses provided to the committee as well as minutes of the meetings. The documentation will remain confidential within the DSMB until the study is unblinded.

9.3.2 Clinical Events Committee

A Clinical Events Committee (CEC) will be created to review and adjudicate each suspected clinical endpoint event without unblinding treatment (including all suspected clinical endpoint events from subjects who are discontinued from study treatment). The CEC will comprise qualified judges, who are not investigators in the study and not otherwise directly associated with the sponsor. The CEC judges will remain blinded to treatment throughout the adjudication process and the study. The CEC-adjudicated data will be used in the final efficacy and safety analyses. The CEC will be described in detail in the CEC Manual of Operations.

9.3.3 LDL-C Monitoring Committee

An independent LDL-C Monitoring Committee (LMC) will be created to periodically review the achieved LDL-C results and advise the Executive Group within the Operations Committee regarding potentially increasing the

targeted number of primary endpoint events if the difference in median LDL-C between treatment groups is less than anticipated. The LMC will be described in detail in the LMC Charter.

9.3.4 Executive Committee

The Executive Committee will be responsible for the overall design, conduct, and supervision of the study, including the development of any protocol amendments. It will adjudicate policy among the various constituencies of the study, and will be responsible for reviewing the progress of the study at regular intervals to ensure subject safety and study integrity. The Executive Committee will comprise designated representatives from DCRI, TIMI, and the sponsor MSP Singapore Company, LLC.

9.3.5 Steering Committee

An IMPROVE-IT Steering Committee will be created to provide clinical guidance on protocol development, study implementation and conduct of the study, and interpretation of results. The Steering Committee will comprise designated representatives from among the Principal Investigators.

9.3.6 Publication Committee

All publications (eg, original manuscripts and abstracts of data and information relating to the IMPROVE-IT clinical study) shall be submitted in advance to the Publication Committee for review according to the procedure described below.

The Publication Committee shall be composed of representatives of the academic and other institutions participating in the study or other recognized thought leaders in the field of ACS (ie, the "Thought Leader Representatives"), TIMI, DCRI, and the sponsor. The Thought Leader Representatives shall be nominated by the Steering Committee and shall be approved by the Executive Committee.

The Publication Committee shall act as an independent body of scientific and medical experts with the following charter:

- The Publications Committee must review and approve all proposed analyses and topics suggested by the investigators and participating institutions in the IMPROVE-IT clinical study, the Executive Committee, Steering Committee, TIMI, DCRI, and MSP Singapore Company, LLC.
- All publications discussing the IMPROVE-IT clinical study data and conclusions must be submitted to the Publication Committee for review and approval prior to submission for presentation or publication.
- All other publications relating to the IMPROVE-IT clinical study shall be submitted to the Publication Committee for review and comment prior to submission for presentation or publication.

All draft publications shall be submitted to the Publication Committee at least 45 days prior to submission to a journal or public presentation.

The Publication Committee shall consider each manuscript proposal with due regard for the scientific merit of the proposed publication. Decisions of the Publication Committee shall be by majority vote.

All manuscripts approved by the Publication Committee shall conform to the Uniform Requirements for Manuscripts Submitted to Biomedical Journals.

10.0INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

10.1 Sponsor

The sponsor of this study is indicated in **Section 1**, Title Page.

10.2 Investigators

Only investigators qualified by training and experience to perform a clinical investigation with Ezetimibe/Simvastatin Combination and simvastatin are selected. The sponsor will contact and select all investigators or coinvestigators (ie, the legally responsible party[ies] at each study site), who, in turn, will select their staff.

A clinical study report (CSR) will be prepared by the sponsor or its qualified designee to describe the results of the study. One of the investigators shall be selected by the sponsor to review the CSR and provide approval of the final CSR in writing. The investigator chosen to review and approve the CSR is to be called the CSR Coordinating Investigator. A second investigator shall be selected as the Alternate CSR Coordinating Investigator. The Alternate CSR Coordinating Investigator is to review and approve the CSR should the first CSR Coordinating Investigator be unable to do so. The sponsor is to select the CSR Coordinating Investigator and Alternate CSR Coordinating Investigator from the investigators using the following criteria:

- Must be the Principal Investigator at a study site actively enrolling subjects and participating in the study;
- Must be willing and capable of completing the necessary reviews and providing approval of the CSR in writing;
- Must have participated in clinical research prior to participating in this current study.

10.3 Central Organizations

Redacted

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10. Cholesterol Treatment Trialists' (CTT) Collaboration. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet. 2005;366(9493):1267–78.

Statistical Data Analysis Plan

A Multicenter, Double-Blind, Randomized Study to Establish the Clinical Benefit and Safety of Vytorin (Ezetimibe/Simvastatin Tablet) vs. Simvastatin Monotherapy in High- Risk Subjects Presenting With Acute Coronary Syndrome (IMProved Reduction of Outcomes: Vytorin Efficacy International Trial – IMPROVE IT)

Protocol: P04103

Prepared by

Redacted

STATISTICAL DATA ANALYSIS PLAN 12 OCT 2012

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Statistical Data Analysis Plan

1 INTRODUCTION

The IMPROVE-IT study is a multi-center, randomized, double-blind, active-control study of subjects with stabilized high-risk acute coronary syndrome (ACS) and LDL-C <125 mg/dL (<3.2 mmol/L) (or <100 mg/dL (<2.6 mmol/L) while receiving prescription lipid-lowering therapy) within 10 days of admittance into a hospital. The study is designed to establish the incremental clinical benefit and safety of ezetimibe (administered as part of Ezetimibe/Simvastatin Combination 10/40 tablet, a single tablet containing ezetimibe 10 mg and simvastatin 40 mg) compared with simvastatin monotherapy in high-risk coronary artery disease subjects and aims to address the fundamental question of whether ezetimibe-mediated incremental reductions of LDL-C translates into a clinical benefit.

The study will enroll up to 18,000 stabilized high-risk ACS subjects. Specifically, eligible patients will be individuals who have presented with ST-segment elevation myocardial infarction (MI), non-ST-segment

elevation MI, or unstable angina within the past 10 days, but have been stabilized since. Subjects will receive randomized, double-blind treatment assignment in a 1:1 ratio to either Ezetimibe/Simvastatin Combination 10/40 or simvastatin 40 mg QD. Randomized treatment assignment will be stratified by three factors:

- Randomized treatment assignment for subjects entering the current study (P04103) from the EARLY-ACS study (P03684): assigned eptifibatide or placebo;
- Statin experience: prior statin use or statin naïve. Enrollment of statinexperienced subjects were limited to <=50% of all subjects within each country;
- High-risk ACS diagnosis: NSTE-ACS or STEMI.

After randomization subjects will have regularly scheduled visits at the end of Month 1 and Month 4, and every 4 months thereafter. Compliant patients whose LDL-C remains >79 mg/dL (>2.0 mmol/L) on 2 consecutive measurements may have the simvastatin dose increased to 80 mg/d, with appropriate monitoring. The study will continue until each subject has been followed for a minimum of 2.5 years and at least one primary endpoint event has been documented in 5,250 subjects. If at least 5,250 subjects do not have at least one documented primary endpoint event within 2.5 years of the completion of enrollment, the study will continue until this number of primary endpoint events has accumulated.

The study is conducted under the direction of the Executive Committee [(1)]. In addition, an independent Data and Safety Monitoring Board (DSMB) is responsible for identifying safety issues and interpreting emerging study data at the interim analysis (see **Section 6** Interim Analyses) and making any recommendations regarding modification or termination of the study confidentially to the Executive Committee chairperson. The Executive Committee decides whether to accept a recommendation from the DSMB to modify or terminate the study. The cause of death, non-fatal MI, unstable angina requiring hospitalization, and non-fatal stroke are adjudicated by Clinical Events Committees (CEC) in a blinded fashion, as outlined in the CEC Charter.

This statistical data analysis plan (DAP) is a comprehensive and detailed description of the strategy, rationale and statistical techniques that will be used to assess the effects of ezetimibe 10mg/day and simvastatin 40 mg/day on clinical outcomes in stabilized ACS subjects.
The two pre-specified interim statistical analyses are the responsibility of the Biostatistics department of the Duke Clinical Research Institute (DCRI). The final statistical analysis of the data obtained from this study is the responsibility of the Biostatistics group of the Sponsor, and will be verified independently by DCRI. The DAP will be approved before the first interim efficacy analysis, which will be performed when approximately 50% of the expected total primary events are available. For the purpose of the final analysis, the official clinical database will not be unblinded until medical/scientific review has been completed, protocol violators have been identified, and the data have been declared clean.

2 OBJECTIVES/HYPOTHESES

Primary Objective:

To evaluate the clinical benefit of Ezetimibe/Simvastatin Combination compared with simvastatin in stabilized high-risk ACS subjects on the occurrence of the composite endpoint of cardiovascular (CV) Death, major coronary events, and non-fatal stroke. Major coronary events include non-fatal MI, documented unstable angina that requires admission into a hospital, and all coronary revascularization with either percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) occurring at least 30 days after randomized treatment assignment.

Secondary Objectives:

a. To evaluate the clinical benefit of Ezetimibe/Simvastatin Combination compared with simvastatin in stabilized high-risk ACS subjects on the occurrence of the composite endpoint of death due to all causes, major coronary events, and non-fatal stroke.

b. To evaluate the clinical benefit of Ezetimibe/Simvastatin Combination compared with simvastatin in stabilized high-risk ACS subjects on the occurrence of the composite endpoint of death due to coronary heart disease (CHD) (CHD death), non-fatal MI, and urgent coronary revascularization with either PCI or CABG occurring at least 30 days after randomization.

c. To evaluate the clinical benefit of Ezetimibe/Simvastatin Combination compared with simvastatin in stabilized high-risk ACS subjects on the composite endpoint of CV death, non-fatal MI, documented unstable angina that requires admission into a hospital, all revascularization (including noncoronary) occurring at least 30 days after randomization, and non-fatal stroke.

Tertiary Objectives:

a. To evaluate the clinical benefit of Ezetimibe/Simvastatin Combination compared with simvastatin in stabilized high-risk ACS subjects on each of the following endpoints analyzed individually: death from any cause, CHD death, CV death, MI (fatal or non-fatal), documented unstable angina that requires admission into a hospital, all coronary revascularization with either PCI or CABG occurring at least 30 days after randomization, urgent coronary revascularization with either PCI or CABG occurring at least 30 days after randomization, all revascularization (including non-coronary) occurring at least 30 days after randomization, stroke (fatal or non-fatal), any cardiovascular event leading to admission into a hospital, and congestive heart failure (CHF) that requires hospitalization occurring at least 30 days after randomization.

b.
To evaluate the proportion of subjects achieving reductions in LDL-C and hsCRP:

1) To evaluate the percentage of subjects achieving endpoint concentrations for both LDL-C of <70 mg/dL and high-sensitivity CReactive Protein (hs-CRP) of <2.0 mg/L following 1 month and 4 months of treatment with Ezetimibe/Simvastatin Combination compared with simvastatin.

2) To evaluate the potential relationship between the risk of occurrence of any primary endpoint event and the concentrations of LDL-C and high sensitivity-C-reactive protein (hs-CRP) following 1 month and 4 months of treatment with Ezetimibe/Simvastatin Combination or simvastatin.

c. To evaluate the safety and tolerability of Ezetimibe/Simvastatin Combination compared with simvastatin.

Primary Hypothesis:

In stabilized high-risk ACS subjects, the administration of Ezetimibe/Simvastatin Combination compared with simvastatin will reduce the incidence of the composite endpoint of CV death, major coronary events (non-fatal MI, documented unstable angina that requires admission into a hospital, and all coronary revascularization with either PCI or CABG occurring at least 30 days after randomized treatment assignment), and non-fatal stroke.

Secondary Hypotheses:

a. In stabilized high-risk ACS subjects, the administration of Ezetimibe/Simvastatin Combination compared with simvastatin will reduce the incidence of the composite endpoint of death due to all causes, major coronary events, and non-fatal stroke.

In stabilized high-risk ACS subjects, the administration of Ezetimibe/Simvastatin Combination compared with simvastatin will reduce the incidence of the composite endpoint of CHD death, non-fatal MI, and urgent coronary revascularization with either PCI or CABG occurring at least 30 days after randomization.

c. In stabilized high-risk ACS subjects, the administration of Ezetimibe/Simvastatin Combination compared with simvastatin will reduce the incidence of the composite endpoint of CV death, nonfatal MI, documented unstable angina that requires

b.
admission into a hospital, all revascularization (including non-coronary) occurring at least 30 days after randomization, and non fatal stroke.

Tertiary Hypotheses:

a. In stabilized high-risk ACS subjects, the administration of Ezetimibe/Simvastatin Combination compared with simvastatin will reduce the incidence of the following endpoints, each analyzed individually: death from any cause, CHD death, CV death, MI (fatal or non-fatal), documented unstable angina that requires admission into a hospital, all coronary revascularization with either PCI or CABG occurring at least 30 days after randomization, urgent coronary revascularization with either PCI or CABG occurring at least 30 days after randomization, all revascularization (including non-coronary) occurring at least 30 days after randomization, stroke (fatal or non-fatal), any cardiovascular event leading to admission into a hospital, and CHF that requires hospitalization occurring at least 30 days after randomization.

To evaluate the proportion of subjects achieving reductions in LDL-C and hsCRP:

1) In stabilized high-risk ACS subjects, the administration of Ezetimibe/Simvastatin Combination compared with simvastatin will result in a greater percentage of subjects achieving both an LDL-C concentration of <70 mg/dL and hs-CRP concentration of <2.0 mg/L following 1 month and 4 months of treatment.
2) In stabilized high-risk ACS subjects, the group of subjects, regardless of treatment, achieving the dual goal of an LDL-C concentration of <70 mg/dL and an hs-CRP concentration of <2.0 mg/dL following 1 month and 4 months of treatment will reduce the incidence of the primary composite endpoint compared with the group of subjects, regardless of treatment, that do not achieve the dual goal for LDL-C and hs-CRP.

c. In stabilized high-risk ACS subjects, Ezetimibe/Simvastatin Combination will be well-tolerated.

b.

3 ENDPOINTS

The clinical endpoint events are specifically defined by the CEC Charter [2] and summarized as follows:

Protocol No. P04103

Primary Endpoint Events and Primary Composite Endpoint	Secondary Composite Endpoint (a)	Secondary Composite Endpoint (b)	Secondary Composite Endpoint (c)	Tertiary Individual Endpoints
CV Death, Major Coronary Events, and Stroke	All Death, Major Coronary Events, and Stroke	CHD Death, Non-fatal MI, and Urgent Coronary Revascularization	CV Death, Vascular Events, and Stroke	All Individual Endpoints[a]
CV Death			CV death	CV death
	Death from any cause			Death from any cause
		CHD death		CHD death
Non-fatal MI[b]	Non-fatal MI[b]	Non-fatal MI[b]	Non-fatal MI[b]	
				MI[b]
Documented unstable angina requiring hospitalization	Documented unstable angina requiring hospitalization		Documented unstable angina requiring hospitalization	Documented unstable angina requiring hospitalization
All coronary revascularization with PCI or CABG[c]	All coronary revascularization with PCI or CABG[c]			All coronary revascularization with PCI or CABG[c]
		Urgent coronary revascularization with PCI or CABG[c]		Urgent coronary revascularization with PCI or CABG[c]
			All revascularization[c]	All revascularization[c]
Non-fatal Stroke[b]	Non-fatal Stroke[b]		Non-fatal Stroke[b]	
				Stroke[b]
				Any CV event leading to hospitalization
				CHF that requires hospitalization[d]
				Dual Goal for LDL-C/hs-CRP[e]

CABG = Coronary Artery Bypass Grafting; CHD = Coronary Heart Disease; CHF = Congestive Heart Failure; CV = Cardiovascular; MI = Myocardial Infarction; PCI = Percutaneous Coronary Intervention

a: All individual endpoints are to be analyzed as a tertiary objective.

b: All MIs and all strokes are to be analyzed individually. However, because each composite endpoint already captures deaths caused by MI or stroke, only non-fatal MIs and non-fatal strokes are components of the composite endpoints.

c: Revascularization must occur at least 30 days after randomization to be considered as a clinical endpoint event.

d: CHF that requires hospitalization must occur at least 30 days after randomization to be considered a clinical endpoint event.

e: Percentage of subjects achieving concentrations of LDL-C <70 mg/dL in addition to hs-CRP <2.0 mg/L following 1 month and 4 months of treatment with Ezetimibe/Simvastatin Combination or simvastatin.

3.1 Primary Endpoints

The primary efficacy endpoint measure is the time from randomization to the first occurrence of one of the following: CV death, major coronary events (non-fatal MI, documented unstable angina that requires admission into a hospital, all coronary revascularization with either PCI or CABG occurring at least 30 days after randomization), or non-fatal stroke.

3.2 Secondary Endpoints

Secondary efficacy endpoint measures include:

a. Time from randomization to the first occurrence of death due to any cause, major coronary events, or non-fatal stroke.
b. Time from randomization to the first occurrence of CHD death, non-fatal MI, or urgent coronary revascularization with either PCI or CABG occurring at least 30 days after randomization.
c. Time from randomization to the first occurrence of CV death, non-fatal MI, documented unstable angina that requires admission into a hospital, all revascularization (including noncoronary) occurring at least 30 days after randomization, and non-fatal stroke.

3.3 Tertiary Endpoints

Tertiary efficacy endpoint measures include:

a. Time from randomization to the first occurrence of the individual endpoint events:
    - death from any cause
    - CHD death
    - CV death
    - MI (fatal or non-fatal)
    - Documented unstable angina that requires admission into a hospital
    - All coronary revascularization with either PCI or CABG occurring at least 30 days after randomization
    - Urgent coronary revascularization with either PCI or CABG occurring at least 30 days after randomization

- All revascularization occurring at least 30 days after randomization (including non-coronary)
- Stroke (fatal or non-fatal)
- Any cardiovascular event leading to admission into a hospital
- CHF that requires hospitalization occurring at least 30 days after randomization.

b. Proportion of subjects achieving reductions in LDL-C and hs-CRP:

1) Percent of subjects achieving concentrations of LDL-C <70 mg/dL in addition to hs-CRP <2.0 mg/L. This will be done at month 1 and month 4.

2) Event rate of the primary endpoint at the end of the study in the group of subjects achieving concentrations of LDL-C <70 mg/dL in addition to hs-CRP <2.0 mg/L and the group that do not achieve the goal for LDLC and hs-CRP, regardless of treatment. This will be done based on the LDL-C and CRP measurements at month 1 and month 4.

4 SUBSETS OF SUBJECTS ANALYZED

The “intention-to-treat” (ITT) population includes all subjects who receive randomized treatment assignment. Specifically, all subjects who receive randomized treatment assignment but never take study drug will be analyzed using the assigned treatment. All other subjects will be analyzed using the actual treatment that they received. Subjects with protocol deviations or violations will be analyzed in the ITT population. All the safety and efficacy data will be analyzed based on the ITT population.

5 STATISTICAL METHODS

Planned Statistical Power and Sample Size

The trial began with a sample size of 10,000 patients with approximately 5000 subjects per treatment group, and the assumption that the expected 15 mg/dl difference in LDL-C between the treatment groups would translate into a 10% reduction in risk at 2 years, and a total of 2955 primary endpoint events were estimated to be needed to show this difference with 90% power. With an enrollment phase of about 2 years, a specified minimum follow-up of 2.5 years, and a 2-year event rate in the control arm of 23.5%, it was estimated that the full trial duration would be no longer than 5 years (60 months).

Based on the information [3] that became available after trial initiation, the Executive Committee felt that it was critical to revisit the statistical assumptions originally proposed. The sample size was changed from an original size of 10,000 subjects to up to 18,000 subjects with trial continuing until accrual of approximately 5250 primary endpoint events and a minimum follow-up of 2.5 years which will maintain trial power at approximately 90%. This sample size is determined from a statistical model approach based on pooled blinded endpoint rates and evaluates the effects of a reduced treatment effect in the first 6 months, enrollment rate, followup duration, lag in event rate reporting, differences in population event rates (STEMI and NSTE), and dropout on power and total event accumulation during the trial. Please refer to the 'Statistical Analysis Plan for Interim Sample Size Re-evaluation' [3] for the details of sample size calculations.

Method of Assigning Study Participants to Treatment Groups

Subjects were randomized to one of the two treatment groups in a 1:1 ratio, according to a computer-generated random code. Specifically, when a subject qualified for randomization, the study center contacted the Central Randomization Service. The Central Randomization Service assigned the subject the next available number within the block that was pre-allocated to the study center prior to the start of the study. Additional blocks could be assigned to the center based on the center's enrollment. Randomized treatment assignment for this study was stratified by the following three factors to obtain balance across the treatment groups:

- Randomized treatment assignment for subjects entering the current study (P04103) from the EARLY-ACS study (P03684): assigned eptifibatide or placebo;
- Statin experience: prior statin use or statin naïve. Enrollment of statinexperienced subjects were limited to <=50% of all subjects within each country;
- High-risk ACS diagnosis: NSTE-ACS or STEMI.

Study Participants Characteristics

Demographic and baseline characteristics of the study population will be summarized and assessed. No formal statistical testing will be performed.

Summary statistics (sample size, mean, median, range, and proportion, when appropriate) will be provided by treatment groups for demographic and baseline variables including:

1. Continuous baseline demographic variables: age (years); body weight (kg); body mass index (kg/m^2).

2. Categorical baseline demographic variables: gender group (female, male); age group (<65/≥65, <75/≥75).

3. Baseline efficacy variables: LDL-C, HDL-C, total-C, Non-HDL-C, TG, Apo B, Apo A-I, Lp (a), LDL-C:HDL-C, total-C:HDL-C and CRP.

4. Baseline stratification variables: Early use of eptifibatide (EARLY-ACS eptifibatide, EARLY-ACS placebo, non-EARLY-ACS), statin experience (prior statin use, statin naïve), High-risk ACS diagnosis (NSTE-ACS, STEMI).

5.1 Analyses of Efficacy

Clinical endpoint events adjudicated by the Clinical Events Committee (CEC) will be used in the final efficacy analyses. The details of the CEC adjudicated events can be found in the CEC Charter [(2)].

The primary efficacy outcome measure is the time from randomization to the first occurrence of one of the following: CV death, major coronary events (non-fatal MI, documented unstable angina that requires admission into a hospital, all coronary revascularization with either PCI or CABG occurring at least 30 days after randomization), or non-fatal stroke. The primary hypothesis is that in stabilized high-risk ACS subjects, the administration of Ezetimibe/Simvastatin Combination compared with simvastatin will reduce the incidence of the composite endpoint of CV death, major coronary events, and non-fatal stroke. This hypothesis will be evaluated using a Cox proportional-hazard model (COX PH model) with covariates of treatment (simvastatin, ezetimibe/simvastatin) and stratification factors (early use of eptifibatide, statin experience, and high-risk ACS diagnosis). Treatment difference will be tested at alpha level of 0.0438 accounting for the two pre-specified interim analyses. Estimates of the hazard ratio and associated 95 percent confidence interval comparing simvastatin with ezetimibe/simvastatin combination will be provided with the use of this model. Event curves by treatment group will be presented based on the Kaplan-Meier estimates.

Since revascularization occurring up to 30 days after randomization is not included in the primary endpoint, a sensitivity analysis by including these events in the primary endpoint will be performed using the same COX PH model specified above.

The hazards proportionality assumption of Cox model for the primary endpoint will be assessed by testing interaction between treatment and follow-up time in the Cox model at a level of 5%. If the proportionality assumption is not satisfied, the estimate of the hazard ratio for the primary endpoint will

be interpreted as an average treatment effect over the time range of the study. An exploratory analysis using nonPH models will be performed for the primary endpoint if the proportionality assumption is not satisfied.

Due to the imbalance between two treatment groups in number of patients titrated to higher statin dose, the treatment effect may be under-estimated. To explore the impact of the titration effect, the same COX PH model specified for the primary endpoint will be performed by including all subjects' non-titrated experience with titrated subjects censored at time of titration.

There are three supportive secondary composite endpoints. The first secondary efficacy outcome measure is the time from randomization until the first occurrence of the composite incidences of death from any cause, non-fatal MI, documented unstable angina that requires admission into a hospital, all coronary revascularization events with either percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) occurring at least 30 days after randomized treatment assignment, and non-fatal stroke. The second secondary efficacy outcome measure is the time from randomization until the first occurrence of the composite incidences of death from coronary heart disease (CHD), non-fatal MI, and urgent coronary revascularization events with either percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) occurring at least 30 days after randomized treatment assignment. The third secondary efficacy outcome measure is the time from randomization until the first occurrence of the composite incidences of CV death, non-fatal MI, documented unstable angina that requires admission into a hospital, all revascularization (including both coronary and non-coronary) occurring at least 30 days after randomized treatment assignment, and non-fatal stroke.

The hypothesis for each secondary endpoint is that Ezetimibe/Simvastatin Combination compared with simvastatin will reduce the incidence of the composite secondary endpoint. Treatment difference will be tested using the same Cox proportional-hazard model specified above for the primary endpoint. Estimates of hazard ratios and associated 95% confidence intervals between the two treatments will be provided with the use of this model. Kaplan-Meier estimates for the time to each of the secondary endpoints will be plotted.

For the individual tertiary endpoint events, the outcomes measure will be the time from randomization to the first occurrence for each of the following: CV death, death from any cause, CHD death, MI (fatal or non-fatal), documented unstable angina that requires admission into a hospital, all revascularization (including both coronary and non-coronary) occurring at least 30 days after randomization, stroke (fatal or non-fatal), and any CV event leading to hospitalization, and CHF that requires hospitalization occurring at least 30 days after randomization. These endpoints measuring outcomes will be analyzed by the same Cox proportional-hazard model specified for the primary endpoint.

For the other tertiary efficacy endpoints, the CMH test adjusting for the stratification factors will be used to compare the two treatment groups with respect to the percent of subjects achieving concentrations of LDL-C<70 mg/dL in addition to hs-CRP<2.0 mg/L achieved at month 1. The primary endpoint in comparison of the group of subjects achieving concentrations of LDL-C<70 mg/dL in addition to hs-CRP <2.0 mg/L achieved at month 1 versus the group that do not achieve the goal for LDL-C and hs-CRP at month 1, regardless of treatment, will be analyzed using a COX PH model with covariate of target goal indicator (achieved goal for both LDL-C<70 mg/dL and hs-CRP <2.0 mg/L, vs. not). These tests will be repeated for LDL-C and CRP achieved at month 4. Please note that these analyses are based on postrandomization classifications.

In addition, the actual, change and percent change from baseline in lipid parameters (LDL-C, HDL-C, total-C, Non-HDL-C, TG, Apo B, Apo A-I, Lp (a), LDL-C:HDL-C, total-C:HDL-C) and CRP will be summarized (N, mean, SD, median, IQR) by treatment group at each scheduled visits when applicable. P-value for treatment difference based on a non-parametric approach using a one-way ANOVA model on the ranks extracting treatment effects will also be provided.

5.1.1 Multiplicity

There is a single primary efficacy endpoint (composite of CV death, major coronary events and non-fatal stroke) and one primary comparison (simvastatin vs. ezetimibe/simvastatin) defined in the primary hypothesis. Hence, no additional adjustment for multiplicity is needed for the primary hypothesis other than accounting for the two pre- specified interim analyses. There are three secondary hypotheses in this study. To adjust for multiplicity, Hochberg's method will be applied to these secondary hypotheses to control the overall alpha level at 0.05. The secondary analyses will be performed only if the primary analysis is statistically significant.

The Hochberg's method is illustrated as follows: order the p-values from the three secondary hypotheses being tested as: $p1 \geq p2 \geq p3$, and let H01, H02, and H03 be the corresponding null hypotheses. Then:

1. If $p1 \leq 0.05/1$ then reject H01, H02, and H03; otherwise
2. If $p2 \leq 0.05/2=0.025$ then reject H02 and H03; otherwise
3. If $p3 \leq 0.05/3=0.017$ then reject H03; otherwise
4. No null hypotheses are rejected.

Analyses of all tertiary and exploratory variables are intended to be supportive of the primary and secondary endpoints. No additional multiplicity adjustment will be applied.

5.1.2 Subgroup Analyses

The following subgroups will be explored. Treatment differences and the associated 95% confidence intervals for the primary endpoint will be provided within each subgroup:

- Gender
- Age (<65, >=65)
- Age (<75, >=75)
- Race (Caucasian, non-Caucasian)
- Diabetes
- Smoking
- Statin experience (prior statin use, statin naïve)
- High-risk ACS diagnosis (NSTE-ACS, STEMI)
- Baseline LDL-C (<=median, >median)
- Baseline HDL-C (<=median, >median)
- Baseline TRIG (<=median, >median)

The consistency of the treatment effect will be assessed for the primary endpoint. For each subgroup, a Cox PH model with terms for treatment, subgroup and treatment-by-subgroup interaction will be performed to test the interaction term. The main treatment effect will not be tested. P-value for testing the interaction term will be provided.

5.1.3 Baseline Definition

Baseline lipids and lipoproteins, vital signs and laboratory safety variables are the last values in the pre-randomization period or randomization visit.

5.1.4 Handling of Missing Data

For time-to-event type efficacy endpoints, patients without experiencing the endpoint events during the study will be censored at the time of last available information. For post baseline lipid data, only available measurement at the time point of interest will be used.

5.2 Safety Analyses

The overall tolerability and safety of ezetimibe 10mg when added to simvastatin 40 mg, based on the intention-to-treat population, will be summarized and assessed by statistical and/or clinical review of all safety parameters, including adverse events, laboratory safety parameters, and clinical safety parameters described in this section.

Adverse Events

Adverse Events (AEs) will be listed and summarized by frequency of occurrence. No statistical inferential tests will be performed except for the incidences of myopathy/rhabdomyolysis, cholecystectomy, cancer, cancer-related death, and gallbladder-related AEs.

Estimates of treatment differences and p-values and 95% confidence intervals based on the method of Miettinen and Nurminen[(5)] will be provided for incidences of myopathy/rhabdomyolysis, cholecystectomy, and gallbladder-related AEs.

For cancer and cancer-related death, a COX PH model with covariate of treatment (simvastatin, ezetimibe/simvastatin) will be performed. Note that the analysis of cancer incidence will exclude non-melanomic skin cancers and cancers that are clinically evident prior to randomization. In addition, cumulative incidence rates of cancer and cancer-related death will also be presented by group.

Clinical Safety

Changes from baseline in the vital signs including pulse, systolic, and diastolic blood pressure will be summarized using descriptive statistics. The Baseline for vital signs is defined as the last available value before Day 3 with Day 1 as the randomization day. No inferential tests will be performed.

Laboratory Safety

Summary statistics by each treatment group will be provided with respect to changes from baseline for laboratory safety parameters at all relevant time points. The Baseline laboratory safety parameter is defined as the last evaluation up through Day 3. No inferential tests will be performed for these laboratory safety parameters except for the “clinically important” elevations in ALT and/or AST, CPK and CPK with muscle symptoms. ALT and/or AST elevations that are considered clinically important are defined as two consecutive elevations greater than or equal to 3 times the upper limit of normal (ULN). For CPK, important single elevations greater than or equal to 10 times the upper limit of normal

are considered clinically important. Estimates of treatment differences and p-values and 95% confidence intervals based on the method of Miettinen and Nurminen[5] will be provided for the incidence of clinically important elevations in ALT and/or AST, CPK and CPK with muscle symptoms.

6 INTERIM ANALYSIS

An independent Data Safety Monitoring Board (DSMB) will review safety data on a regular basis according to the schedule specified in the DSMB charter. An independent Duke Clinical Research Institute (DCRI) statistician will be the only individual with access to the randomization code and results. This independent statistician is not involved in the day-to-day project activities. The DCRI study personnel, Executive Committee, Steering Committee, and sponsors will remain blinded.

Two pre-specified interim efficacy analyses will be performed when approximately 50% and 75% of the expected total primary events are available. The primary analysis will be based on the adjudicated events using the same COX PH model specified for the primary endpoint. Supportive analyses will be performed based on both adjudicated and un-adjudicated events. The O'Brien-Fleming methodology will be implemented to protect the overall type I error of 0.05 using the software East. Specifically, a nominal alpha level of 0.003 will be used for the first interim analysis (50% of events) and a nominal alpha level of 0.0184 will be used for the second interim analysis (75% of events). Overwhelming efficacy for early study termination minimally requires significance for the primary efficacy endpoint at the specified nominal significance levels and a directionally consistent reduction in total mortality. For the final analysis, the primary endpoint will be tested at a nominal alpha level of 0.0438. Note that if the number of events at the interim analysis does not exactly match the pre-specified number (50% or 75% of events), the nominal alpha level will be adjusted according to the Lan-DeMets implementation of the O'Brien-Fleming boundary and will be included in the interim report. Any change to alpha levels at the interim analyses may also affect the nominal alpha level for the final analysis.
Details for the interim analyses are provided in the DSMB charter [4].

After the second protocol planned interim analysis, the DSMB asked for an additional review of the data in the early 2013 timeframe. Although not explicitly stated in correspondence from the DSMB, it may be reasonable to assume that this review will include an unblinded analysis of efficacy data that would include early stopping of the trial for efficacy. In this case, the prespecified Lan DeMets approximation to the O'Brien-Fleming methodology will continue to be used to protect the overall type I error of 0.05, using the software EAST. For example, if a single additional unblinded efficacy analysis beyond the two pre-specified in the protocol, is

performed at 85% of events, a nominal alpha level of 0.0242 would be used and the final analysis would be tested at a nominal alpha level of 0.0402.

7 REFERENCES

1. Protocol of IMPROVE IT Study (Protocol No. P04103)
2. Clinical Endpoints Committee, Manual of Operations, IMPROVE IT Study
3. Statistical Analysis Plan for Interim Sample Size Re-evaluation, IMPROVE IT Study
4. Data Safety Monitoring Board Charter, IMPROVE IT Study
5. Miettinen O, Nurminen M. Comparative analysis of two rates. Statistics in Medicine 1985; 4: 213-226.

MEMO

DATE: October 15, 2014 (Amended) February 28, 2013 (Original)

TO: Redacte d

FROM: Redacted

CC: Redacted

SUBJECT: Statistical Considerations for MK-0653A P04103 IMPROVE-IT Study

The purpose of this memo is to describe statistical considerations to be used for additional exploratory analyses and to provide clarification of statistical rules in MK- 0653A Protocol 04103 (IMPROVE-IT Study). This document provides supplements to the analyses that were specified in the protocol and Statistical Analysis Plan.

As specified in the Statistical Analysis Plan (SAP) (Section 5.1.1), the analyses of all tertiary and exploratory variables are intended to be supportive of the primary and secondary endpoints and no multiplicity adjustment was planned. Similarly, the exploratory analyses specified in this memo are considered hypothesis generating and may suffer from inflation of both the false positive and false negative rates like those in the SAP, and likewise will not employ any adjustments. It is important to recognize that the IMPROVE-IT study was not specifically designed to address many of these analyses, and therefore all results need to be interpreted carefully in the context of the many exploratory analyses that are being performed.

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1. LANDMARK ANALYSES

Landmark analyses will be performed on the primary composite endpoint and three key secondary composite endpoints in order to explore treatment effects before and after the 6-month time point following randomization. Six months was selected due to the potential for a delayed treatment effect in this time frame. It is important to recognize that should any/all of the primary and three key secondary composite endpoints meet the proportional hazard assumption, then the single best estimate of treatment effect for any subset of time for this study is the overall hazard ratio. All other estimates may be subject to bias and/or the increased noise associated with subgroup analyses. Crude event rates and annualized event rates will be reported by time period. Kaplan-Meier estimates will also be provided. The hazard ratio (EZ/Simva vs. Simva) and confidence interval (CI) for each time period will be calculated using a single Cox proportional hazards model employing all the data as per the study design, with terms for treatment and interaction between time period and treatment, as well as stratification factors (participation in EARLY ACS trial, prescription lipid-lowering experience, and high-risk ACS diagnosis). The p-value for interaction between time period and treatment will test the potential difference in treatment effect between the first 6 months and subsequent months of the trial. Kaplan-Meier (KM) curves for each treatment group from randomization to the last visit will be plotted with a vertical reference line at the 6-month time point. The plot will be annotated with the hazard ratio and 95% CI from each time period. A second display of KM curves by treatment group will be provided from 6 months to the last visit and will exclude subjects who experience an event prior to the landmark time. The plot will begin at 0% incidence on the y-axis and 6 months on the x- axis. Note that both KM displays may be affected by the choice of an arbitrary time point. In addition, the second KM display represents a non-randomized comparison because of the exclusion of subjects who had an event or were censored prior to month 6. For this reason, caution should be exercised in interpretation, as the results may be influenced by the bias introduced by performing a non-randomized comparison and/or by censoring mechanisms no longer independent of the outcome.

In addition to the landmark analyses specified above, the first occurrence of the primary composite endpoint for each subject will also be summarized by treatment group and year analogous to Figure 2 in the Heart Protection Study (HPS) 11-year follow-up trial publication (Lancet 2011; 378: 2013-20). Similar to the HPS trial, the denominators for each year will be based on the number of subjects at risk of a first event at the start of each year.

Statistical Considerations for MK-0653A P04103 IMPROVE-IT Study

Table 1.1
Landmark Analysis of Primary Composite Endpoint:
Cardiovascular Death, Major Coronary Event†, or Non-fatal Stroke

Primary Composite Endpoint	EZ/Simva				Simva				Treatment Comparison
	n	(%)‡	Annual %§	KM% (95% CI)‖	n	(%)‡	Annual %§	KM% (95% CI)‖	HR (95% CI)¶
No. of subjects at risk ††	xxxx				xxxx				
Events from Randomization to 6 months	xxxx	x.xx	x.xx	x.xx (x.xx , x.xx)	xxxx	x.xx	x.xx	x.xx (x.xx , x.xx)	x.xx (x.xx , x.xx)
No. of subjects at risk ‡‡	xxxx				xxxx				
Events from 6 months to Last visit	xxxx	x.xx	x.xx	x.xx (x.xx , x.xx)	xxxx	x.xx	x.xx	x.xx (x.xx , x.xx)	x.xx (x.xx , x.xx)
p-Value for interaction between time period and treatment: x.xxx									

†Major Coronary Event = Non-fatal MI, documented UA requiring hospitalization, or coronary revascularization with PCI or CABG ≥ 30 days after randomization.

‡Crude number of events (n) and percentage (%).

§Annual% = total events / time at risk in years.

‖ Kaplan-Meier estimate at 6 months for events from randomization to 6 months; KM estimate at 7 years for events from 6 mos. to last visit.

¶ Hazard ratio (EZ/Simva vs. Simva) and confidence interval from Cox proportional hazard model with covariates of the stratification factors (EARLY ACS trial, chronic prescription lipid-lowering experience, and high-risk ACS diagnosis), treatment, and interaction between time period and treatment. †† Number of subjects in protocol-defined ITT population. ‡‡ Number of subjects in protocol-defined ITT population, excluding subjects with an event or censored prior to 6 months.

AdditionalTables using T able1.1 T emplate (and Figures)

Figure 1.1a: Landmark Analysis of Primary Composite Endpoint (CV Death, Major Coronary Event, or Non-fatal Stroke)
Figure 1.1b: Landmark Analysis of Primary Composite Endpoint (CV Death, Major Coronary Event, or Non-fatal Stroke), Excluding Subjects with an Event Prior to Landmark
Table 1.2: Landmark Analysis of Secondary Composite Endpoint (Death Due to any Cause, Major Coronary Event, or Non-fatal Stroke)
Figure 1.2a: Landmark Analysis of Secondary Composite Endpoint (Death Due to any Cause, Major Coronary Event, or Non-fatal Stroke)
Figure 1.2b: Landmark Analysis of Secondary Composite Endpoint (Death Due to any Cause, Major Coronary Event, or Non-fatal Stroke), Excluding Subjects with an Event Prior to Landmark
Table 1.3: Landmark Analysis of Secondary Composite Endpoint (CHD Death, Non-fatal MI, or Urgent Coronary Revascularization with PCI or CABG after 30 days)
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Figure 1.4b: Landmark Analysis of Secondary Composite Endpoint (CV Death, Non-fatal MI, Documented UA Requiring Hospitalization, All Revascularization, or Non-fatal Stroke), Excluding Subjects with an Event Prior to Landmark

2. ANALYSIS OF RECURRENT EVENTS

An analysis will be performed for the following endpoints to explore the potential benefit of EZ/Simva compared to Simva in preventing recurrent events:

- Protocol-specified primary composite endpoint
- Three protocol-specified key secondary composite endpoints
- A composite endpoint of CV death, non-fatal MI, and non-fatal stroke (not specified in the protocol)

The marginal approach of Wei, Lin, and Weissfeld (WLW method) will be used to fit a Cox model including terms for treatment and stratification factors (index for number of recurrent events, participation in EARLY ACS trial, prescription lipid-lowering experience, and high-risk ACS diagnosis). This methodology includes all subjects in the protocol-defined ITT analysis assuming each subject is simultaneously at risk for each type of event; therefore, randomization is maintained allowing for valid estimation for recurrent events. Note that because death in some form is one of the components of each of the composite endpoints being explored, an imbalance in deaths between treatment groups may lead to biased results in the recurrent events analysis since death precludes further accrual of events.

Time to first, second, third, and fourth event will be compared between Simva and EZ/Simva groups. The estimates of the hazard ratios (EZ/Simva vs. Simva) and 95% confidence intervals for the first four events will be reported and a test of equality of hazard ratio will be performed. If the test of the equality of hazard ratio is not rejected, then an average hazard ratio across the first four events will be reported and statistical testing performed. A summary of recurrent events for the individual components of the composite endpoints will be examined (1st event, 2nd event, etc.).

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Table 2.1
Analysis of Recurrent Events of the Primary Composite Endpoint
(CV Death, Major Coronary Event†, or Non-fatal Stroke)
(Protocol-defined ITT Population)

	EZ/Simva (N=xxxx)	Simva (N=xxxx)		
	Number of Events	Number of Events	Hazard Ratio‡ (95% CI)	p-Value‡
Number of subjects with 1st event	xxxx	Xxxx	x.xx (x.xx, x.xx)	-
Number of subjects with 2nd event	xxxx	Xxxx	x.xx (x.xx, x.xx)	-
Number of subjects with 3rd event	xxxx	Xxxx	x.xx (x.xx, x.xx)	-
Number of subjects with 4th event	xxxx	Xxxx	x.xx (x.xx, x.xx)	-
Test of equality of hazard ratio across first 4 events				x.xxx
Average hazard ratio across first 4 events			x.xx (x.xx, x.xx)	x.xxx

† Major Coronary Event = Non-fatal MI, documented UA requiring hospitalization, or coronary revascularization with PCI or CABG ≥ 30 days after randomization.

‡ Hazard ratio (EZ/Simva vs. Simva), confidence interval, and p-Values based on WLW method with covariates of the stratification factors (EARLY ACS trial, prescription lipid-lowering experience, high-risk ACS diagnosis) and treatment.

Statistical Considerations for MK-0653A P04103 IMPROVE-IT Study

Additional Tables using Table 2.1T emplate

Table2.2: Analysis of Recurrent Events of Secondary Composite Endpoint (Death Due to any Cause, Major Coronary Event, or Non-fatal Stroke) (Protocol-defined ITT Population)

Table 2.3: Analysis of Recurrent Events of Secondary Composite Endpoint (CHD Death, Non-fatal MI, or Urgent Coronary Revascularization with PCI or CABG after 30 days) (Protocol-defined ITT Population)

Table 2.4: Analysis of Recurrent Events of Secondary Composite Endpoint (CV Death, Non-fatal MI, Documented UA Requiring Hospitalization, All Revascularization, or Non-fatal Stroke) (Protocol-defined ITT Population)

Table 2.5: Analysis of Recurrent Events of CV Death, MI, and Stroke (Protocol-defined ITT Population)

Table 2.6
Summary of Recurrent Events of the Primary Composite Endpoint:
CV Death, Major Coronary Event†, or Non-fatal Stroke
(Protocol-defined ITT Population)

	1st Event		2nd Event		3rd Event		4th Event		≥ 5 Events		Total Events	
Primary Composite Endpoint	EZ/Simva	Simva	EZ/Simva	Simva	EZ/Simva	Simva	EZ/Simva	Simva	EZ/Simva	Simva	EZ/Simva	Simva
Any	120	xxx xxx	100 xxx	xxx	45 xxx	xxx	40 xxx	xxx	42 xxx	xxx	347	xxx
CV Death	30 10	xxx xxx	xxx xxx	xxx xxx	xxx	xxx xxx	xxx	xxx xxx	xxx	xxx xxx	xxx	xxx xxx
Non-fatal MI	30			xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx xxx	xxx
Documented UA requiring hosp.		xxx	xxx									
All coronary revasc. with PCI or CABG	30			xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx
Non-fatal Stroke		xxx	xxx									
	20			xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx

† Major Coronary Event = Non-fatal MI, documented UA requiring hospitalization, or coronary revascularization with PCI or CABG ≥ 30 days after randomization.

Additional Tables using Table 2.6T emplate

Table 2.7: Summary of Recurrent Events of Secondary Composite Endpoint (Death Due to any Cause, Major Coronary Event, or Non-fatal Stroke) (Protocol-defined ITT Population)

Table 2.8: Summary of Recurrent Events of Secondary Composite Endpoint (CHD Death, Non-fatal MI, or Urgent Coronary Revascularization with PCI or CABG after 30 days) (Protocol-defined ITT Population)

Table 2.9: Summary of Recurrent Events of Secondary Composite Endpoint (CV Death, Non-fatal MI, Documented UA Requiring Hospitalization, All Revascularization, or Non-fatal Stroke) (Protocol-defined ITT Population)

Table 2.10: Summary of Recurrent Events of CV Death, MI, and Stroke (Protocol-defined ITT Population)

3. ANALYSIS OF TREATMENT EFFECT BY LDL-C REDUCTION

To evaluate the relationship between LDL-C reduction and treatment effect in IMPROVE-IT, and to facilitate comparison with observations in previous randomized trials (as reported by the Cholesterol Treatment Trialists (CTT) Collaboration [Lancet 2010 Nov 13; 376: 1670-81]), the observed reduction in major vascular events (and other composites as defined below) per 1.0 mmol/L reduction in LDL-C will be assessed. The following steps will be taken:

- Define and summarize a specific endpoint composite for IMPROVE-IT that is as consistent as possible with the CTT "major vascular event" (MVE) category; the latter category is comprised of major coronary event (non-fatal MI and coronary heart disease [CHD] death), coronary revascularization, and stroke.

- Perform an analysis of this "MVE" composite endpoint using statistical methodology consistent with the analysis of the IMPROVE-IT primary composite endpoint. Unweighted hazard ratios (EZ/Simva vs. Simva) and confidence intervals will be calculated using a Cox proportional hazards model with a term for treatment and stratification factors (participation in EARLY ACS trial, prescription lipid-lowering experience, and high-risk ACS diagnosis).

- Calculate the between-group LDL-C reduction at one year (± 2 mos). In the event of multiple LDL-C values, the value closest to the one year visit will be selected for analysis. Hazard ratios (EZ/Simva vs. Simva) weighted per 1 mmol/L LDL-C reduction will be calculated by dividing the natural log of the observed unweighted hazard ratio by the between-group LDL-C reduction at one year and then exponentiating the result. Data will be presented in the format of Table 3.1 below. A forest plot similar to Figure 2 reported by the CTT Collaboration (Lancet 2010 Nov 13) will be provided, using the IMPROVE-IT data. 95% confidence intervals will be reported for composite endpoints and 99% confidence intervals will be reported for individual components.

The relationship between LDL-C reduction and treatment effect will be evaluated for the IMPROVE-IT primary composite endpoint (Table 3.3) using the same algorithm as described for the MVE composite endpoint. In addition to LDL-C reduction at one year, both endpoints will also be analyzed based on the between-group LDL-C reduction using a time-weighted average over the trial.

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Table 3.1
Analysis of the Major Vascular Event (MVE) Composite Endpoint per CTT:
Major Coronary Event, Coronary Revascularization, or Stroke
Per 1.0 mmol/L LDL-C Reduction at One Year (Protocol-defined ITT Population)

	EZ/Simva				Simva					
	n	(%) †	Annual % ‡	KM% (95% CI) §	n	(%) †	Annual % ‡	KM% (95% CI) §	HR (CI) ǁ (Unweighted)	HR (CI) ¶ (Per 1 mmol/L Reduction in LDL-C)
MVE Composite Endpoint	xxxx	(xx.x)	xx.x	xx.x (xx.x, xx.x)	xxxx	(xx.x)	xx.x	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)
Any Major Coronary Event (CTT)	xxxx	(xx.x)	xx.x	xx.x (xx.x, xx.x)	xxxx	(xx.x)	xx.x	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)
Non-fatal MI	xxxx	(xx.x)	xx.x	xx.x (xx.x, xx.x)	xxxx	(xx.x)	xx.x	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)
CHD Death	xxxx	(xx.x)	xx.x	xx.x (xx.x, xx.x)	xxxx	(xx.x)	xx.x	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)
Any Coronary Revasc.	xxxx	(xx.x)	xx.x	xx.x (xx.x, xx.x)	xxxx	(xx.x)	xx.x	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)
CABG	xxxx	(xx.x)	xx.x	xx.x (xx.x, xx.x)	xxxx	(xx.x)	xx.x	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)
PCI	xxxx	(xx.x)	xx.x	xx.x (xx.x, xx.x)	xxxx	(xx.x)	xx.x	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)
Any Stroke	xxxx	(xx.x)	xx.x	xx.x (xx.x, xx.x)	xxxx	(xx.x)	xx.x	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)
Ischemic ††	xxxx	(xx.x)	xx.x	xx.x (xx.x, xx.x)	xxxx	(xx.x)	xx.x	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)
Hemorrhagic	xxxx	(xx.x)	xx.x	xx.x (xx.x, xx.x)	xxxx	(xx.x)	xx.x	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)
Unknown	xxxx	(xx.x)	xx.x	xx.x (xx.x, xx.x)	xxxx	(xx.x)	xx.x	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)

If a subject has multiple events, only the first event contributing to the composite endpoint is counted in the component row of the table. †
Crude number of events (n) and percentage (%).
‡ Annual % = total events / time at risk in years. § Kaplan-Meier estimate and confidence interval.
‖
Hazard ratio (EZ/Simva vs. Simva) and confidence interval from Cox proportional hazard model with covariates of the stratification factors (EARLY ACS trial, chronic prescription lipid-lowering experience, and high-risk ACS diagnosis) and treatment.
¶
Hazard ratio (EZ/Simva vs. Simva) calculated as the unweighted HR divided by the between-group LDL-C reduction at one year. ††
Non-hemorrhagic.
HR confidence intervals are reported as 95% CI for composite endpoints and 99% CI for individual components.

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AdditionalT ables and Figures using Table 3.1T emplate

Figure 3.1: Analysis of the Major Vascular Events Composite Endpoint (per CTT) Per 1.0 mmol/L LDL-C Reduction at One Year (Protocol-defined ITT Population)

Table 3.2: Analysis of the Major Vascular Events Composite Endpoint (per CTT) Per 1.0 mmol/L LDL-C Reduction Averaged Over the Trial (Protocol-defined ITT Population)

Figure 3.2: Analysis of the Major Vascular Events Composite Endpoint (per CTT) Per 1.0 mmol/L LDL-C Reduction Averaged Over the Trial (Protocol-defined ITT Population)

Table 3.1.1: Analysis of the Major Vascular Events Composite Endpoint (per CTT) Per 1.0 mmol/L LDL-C Reduction at One Year (On-Treatment Analysis with Events Censored 30 Days after Study Drug Discontinuation)

Table 3.2.1: Analysis of the Major Vascular Events Composite Endpoint (per CTT) Per 1.0 mmol/L LDL-C Reduction Averaged Over the Trial (On-Treatment Analysis with Events Censored 30 Days after Study Drug Discontinuation)

Table 3.3
Analysis of the IMROVE-IT Primary Composite Endpoint:
CV Death, Major Coronary Event, or Non-fatal Stroke
Per 1.0 mmol/L LDL-C Reduction at One Year
(Protocol-defined ITT Population)

	EZ/Simva				Simva					
	n	(%) †	Annual % ‡	KM% (95% CI) §	n	(%) †	Annual % ‡	KM% (95% CI) §	HR (CI) ǁ (Unweighted)	HR (CI) ¶ (Per 1 mmol/L Reduction in LDL-C)
Primary Composite Endpoint	xxxx	(xx.x)	xx.x	xx.x (xx.x, xx.x)	xxxx	(xx.x)	xx.x	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)
Any CV Death	xxxx	(xx.x)	xx.x	xx.x (xx.x, xx.x)	xxxx	(xx.x)	xx.x	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)
Any Major Coronary Event	xxxx	(xx.x)	xx.x	xx.x (xx.x, xx.x)	xxxx	(xx.x)	xx.x	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)
Non-fatal MI	xxxx	(xx.x)	xx.x	xx.x (xx.x, xx.x)	xxxx	(xx.x)	xx.x	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)
Unstable Angina Requiring Hospitalization	xxxx	(xx.x)	xx.x	xx.x (xx.x, xx.x)	xxxx	(xx.x)	xx.x	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)
Coronary Revascularization	xxxx	(xx.x)	xx.x	xx.x (xx.x, xx.x)	xxxx	(xx.x)	xx.x	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)
Any Non-fatal Stroke	xxxx	(xx.x)	xx.x	xx.x (xx.x, xx.x)	xxxx	(xx.x)	xx.x	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)

If a subject has multiple events, only the first event contributing to the composite endpoint is counted in the component row of the table. †
Crude number of events (n) and percentage (%).
‡ Annual % = total events / time at risk in years. § Kaplan-Meier estimate and confidence interval.
‖
Hazard ratio (EZ/Simva vs. Simva) and confidence interval from Cox proportional hazard model with covariates of the stratification factors (EARLY ACS trial, prescription lipid-lowering experience, and high-risk ACS diagnosis) and treatment.
¶
Hazard ratio (EZ/Simva vs. Simva) calculated as the unweighted HR divided by the between-group LDL-C reduction at one year.
HR confidence intervals are reported as 95% CI for composite endpoints and 99% CI for individual components.

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Additional Tables and Figures using Table 3.3 Template

Figure 3.3: Analysis of the IMPROVE-IT Primary Composite Endpoint (per CTT) Per 1.0 mmol/L LDL-C Reduction at One Year (Protocol-defined ITT Population)

Table 3.4: Analysis of the IMPROVE-IT Primary Composite Endpoint (per CTT) Per 1.0 mmol/L LDL-C Reduction Averaged Over the Trial (Protocol-defined ITT Population)

Figure 3.4: Analysis of the IMPROVE-IT Primary Composite Endpoint (per CTT) Per 1.0 mmol/L LDL-C Reduction Averaged Over the Trial (Protocol-defined ITT Population)

Table 3.3.1: Analysis of the IMPROVE-IT Primary Composite Endpoint (per CTT) Per 1.0 mmol/L LDL-C Reduction at One Year (On-Treatment Analysis with Events Censored 30 Days after Study Drug Discontinuation)

Table 3.4.1: Analysis of the IMPROVE-IT Primary Composite Endpoint (per CTT) Per 1.0 mmol/L LDL-C Reduction Averaged Over the Trial (On-Treatment Analysis with Events Censored 30 Days after Study Drug Discontinuation)

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4. SUBGROUP ANALYSES

In addition to the subgroups specified in the Statistical Analysis Plan (Section 5.1.2), the primary endpoint of the study will be explored with respect to the following additional covariates:

- Diagnosis of hypertension at baseline (Yes, No)
- Percutaneous coronary intervention (PCI) in relation to the index ACS event (Yes, No)
- Baseline creatinine clearance (<60, ≥60 to <90, ≥90 ml/min)
- Participation in EARLY acute coronary syndrome (ACS) trial (Yes, No)
- Baseline Non-HDL-C (≤ median, > median mg/mL)
- Baseline CRP (≤2, >2 mg/L)
- Baseline LDL-C (quartiles)
- REACH score (quartiles)

Subgroup analyses will be performed in the protocol-defined intention-to-treat (ITT) population and using a Cox proportional hazards model with terms for treatment, subgroup, and treatment-by-subgroup interaction and stratification factors (participation in EARLY ACS trial, prescription lipid-lowering experience, and high-risk ACS diagnosis). The hazard ratio and 95% confidence interval will be provided within each subgroup and the p-value for testing treatment-by-subgroup interaction will be reported (Table 4.1)

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Table 4.1
Subgroup Analysis of Primary Composite Endpoint
(Protocol-defined ITT Population)

	EZ/Simva (N=xxxx)				Simva (N=xxxx)				Treatment Comparison	
	n	(%) [‡]	Annual % [§]	KM% (95% CI) [‖]	n	(%) [‡]	Annual % [§]	KM% (95% CI) [‖]	HR (95% CI) [¶]	p-Value [¶]
Gender [††]										
Male	xxxx	(xx.x)	xx.x	xx.x (xx.x, xx.x)	xxx	(xx.x)	xx.x	xx.x (xx.x, xx.x)	x.xx (x.xx, x.xx)	x.xxx
Female	xxxx	(xx.x)	xx.x	xx.x (xx.x, xx.x)	xxx	(xx.x)	xx.x	xx.x (xx.x, xx.x)	x.xx (x.xx, x.xx)	
Age Group 1 (years) [††]										
< 65	xxxx	(xx.x)	xx.x	xx.x (xx.x, xx.x)	xxx	(xx.x)	xx.x	xx.x (xx.x, xx.x)	x.xx (x.xx, x.xx)	x.xxx
≥ 65	xxxx	(xx.x)	xx.x	xx.x (xx.x, xx.x)	xxx	(xx.x)	xx.x	xx.x (xx.x, xx.x)	x.xx (x.xx, x.xx)	
Age Group 2 (years) [††]										
< 75	xxxx	(xx.x)	xx.x	xx.x (xx.x, xx.x)	xxx	(xx.x)	xx.x	xx.x (xx.x, xx.x)	x.xx (x.xx, x.xx)	x.xxx
≥ 75	xxxx	(xx.x)	xx.x	xx.x (xx.x, xx.x)	xxx	(xx.x)	xx.x	xx.x (xx.x, xx.x)	x.xx (x.xx, x.xx)	
Race [††]										
Caucasian	xxxx	(xx.x)	xx.x	xx.x (xx.x, xx.x)	xxx	(xx.x)	xx.x	xx.x (xx.x, xx.x)	x.xx (x.xx, x.xx)	x.xxx
Non-caucasian	xxxx	(xx.x)	xx.x	xx.x (xx.x, xx.x)	xxx	(xx.x)	xx.x	xx.x (xx.x, xx.x)	x.xx (x.xx, x.xx)	
Diabetes [††]										
Yes	xxxx	(xx.x)	xx.x	xx.x (xx.x, xx.x)	xxx	(xx.x)	xx.x	xx.x (xx.x, xx.x)	x.xx (x.xx, x.xx)	x.xxx
No	xxxx	(xx.x)	xx.x	xx.x (xx.x, xx.x)	xxx	(xx.x)	xx.x	xx.x (xx.x, xx.x)	x.xx (x.xx, x.xx)	

Current Smoker[††]									
Yes	xxxx	(xx.x)	xx.x	xx.x (xx.x, xx.x)	xxx	(xx.x)	xx.x	xx.x (xx.x, xx.x)	x.xx (x.xx, x.xx)	x.xxx
No	xxxx	(xx.x)	xx.x	xx.x (xx.x, xx.x)	xxx	(xx.x)	xx.x	xx.x (xx.x, xx.x)	x.xx (x.xx, x.xx)	
Diagnosis of Hypertension									
Yes	xxxx	(xx.x)	xx.x	xx.x (xx.x, xx.x)	xxx	(xx.x)	xx.x	xx.x (xx.x, xx.x)	x.xx (x.xx, x.xx)	x.xxx
No	xxxx	(xx.x)	xx.x	xx.x (xx.x, xx.x)	xxx	(xx.x)	xx.x	xx.x (xx.x, xx.x)	x.xx (x.xx, x.xx)	
PCI									
Yes	xxxx	(xx.x)	xx.x	xx.x (xx.x, xx.x)	xxx	(xx.x)	xx.x	xx.x (xx.x, xx.x)	x.xx (x.xx, x.xx)	x.xxx
No	xxxx	(xx.x)	xx.x	xx.x (xx.x, xx.x)	xxx	(xx.x)	xx.x	xx.x (xx.x, xx.x)	x.xx (x.xx, x.xx)	
Baseline Creatinine Clearance (ml/min)									
<60	xxxx	(xx.x)	xx.x	xx.x (xx.x, xx.x)	xxx	(xx.x)	xx.x	xx.x (xx.x, xx.x)	x.xx (x.xx, x.xx)	x.xxx
≥60 to <90	xxxx	(xx.x)	xx.x	xx.x (xx.x, xx.x)	xxx	(xx.x)	xx.x	xx.x (xx.x, xx.x)	x.xx (x.xx, x.xx)	
≥90	xxxx	(xx.x)	xx.x	xx.x (xx.x, xx.x)	xxx	(xx.x)	xx.x	xx.x (xx.x, xx.x)	x.xx (x.xx, x.xx)	

Table 4.1
Subgroup Analysis of Primary Composite Endpoint
(Protocol-defined ITT Population)

	EZ/Simva (N=xxxx)				Simva (N=xxxx)			Treatment Comparison	
	n	(%) [‡]	Annual % [§]	KM% (95% CI) [‖]	n (%) [‡]	Annual % [§]	KM% (95% CI) [‖]	HR (95% CI) [¶]	p-Value [¶]
Participation in EARLY ACS Trial									
Yes, eptifibatide	xxxx	(xx.x)	xx.x	xx.x (xx.x, xx.x)	xxx (xx.x)	xx.x	xx.x (xx.x, xx.x)	x.xx (x.xx, x.xx)	x.xxx
Yes, placebo	xxxx	(xx.x)	xx.x	xx.x (xx.x, xx.x)	xxx (xx.x)	xx.x	xx.x (xx.x, xx.x)	x.xx (x.xx, x.xx)	
No	xxxx	(xx.x)	xx.x	xx.x (xx.x, xx.x)	xxx (xx.x)	xx.x	xx.x (xx.x, xx.x)	x.xx (x.xx, x.xx)	
Prescription Lipid-Lowering (PLL) Experience									
Prior PLL Therapy at Entry	xxxx	(xx.x)	xx.x	xx.x (xx.x, xx.x)	xxx (xx.x)	xx.x	xx.x (xx.x, xx.x)	x.xx (x.xx, x.xx)	x.xxx
No PLL Therapy at Entry	xxxx	(xx.x)	xx.x	xx.x (xx.x, xx.x)	xxx (xx.x)	xx.x	xx.x (xx.x, xx.x)	x.xx (x.xx, x.xx)	
Statin Experience [††]									
Statin Therapy at Entry	xxxx	(xx.x)	xx.x	xx.x (xx.x, xx.x)	xxx (xx.x)	xx.x	xx.x (xx.x, xx.x)	x.xx (x.xx, x.xx)	x.xxx
No Statin Therapy at Entry	xxxx	(xx.x)	xx.x	xx.x (xx.x, xx.x)	xxx (xx.x)	xx.x	xx.x (xx.x, xx.x)	x.xx (x.xx, x.xx)	
High-risk ACS Diagnosis [††]									
NSTE-ACS	xxxx	(xx.x)	xx.x	xx.x (xx.x, xx.x)	xxx (xx.x)	xx.x	xx.x (xx.x, xx.x)	x.xx (x.xx, x.xx)	x.xxx
STEMI	xxxx	(xx.x)	xx.x	xx.x (xx.x, xx.x)	xxx (xx.x)	xx.x	xx.x (xx.x, xx.x)	x.xx (x.xx, x.xx)	
Baseline LDL-C (mg/dL) [††]									
≤ {Median}	xxxx	(xx.x)	xx.x	xx.x (xx.x, xx.x)	xxx (xx.x)	xx.x	xx.x (xx.x, xx.x)	x.xx (x.xx, x.xx)	x.xxx
> {Median}	xxxx	(xx.x)	xx.x	xx.x (xx.x, xx.x)	xxx (xx.x)	xx.x	xx.x (xx.x, xx.x)	x.xx (x.xx, x.xx)	
Baseline LDL-C (mg/dL) [††]									
{1st quartile}	xxxx	(xx.x)	xx.x	xx.x (xx.x, xx.x)	xxx (xx.x)	xx.x	xx.x (xx.x, xx.x)	x.xx (x.xx, x.xx)	x.xxx
{2nd quartile}	xxxx	(xx.x)	xx.x	xx.x (xx.x, xx.x)	xxx (xx.x)	xx.x	xx.x (xx.x, xx.x)	x.xx (x.xx, x.xx)	

{3rd quartile}	xxxx	(xx.x)	xx.x	xx.x (xx.x, xx.x)	xxx	(xx.x)	xx.x	xx.x (xx.x, xx.x)	x.xx (x.xx, x.xx)	
{4th quartile}	xxxx	(xx.x)	xx.x	xx.x (xx.x, xx.x)	xxx	(xx.x)	xx.x	xx.x (xx.x, xx.x)	x.xx (x.xx, x.xx)	
Baseline LDL-C (mg/dL) by PLL										
Therapy Experience										
Prior PLL Therapy ≤{Median}	xxxx	(xx.x)	xx.x	xx.x (xx.x, xx.x)	xxx	(xx.x)	xx.x	xx.x (xx.x, xx.x)	x.xx (x.xx, x.xx)	x.xxx
Prior PLL Therapy >{Median}	xxxx	(xx.x)	xx.x	xx.x (xx.x, xx.x)	xxx	(xx.x)	xx.x	xx.x (xx.x, xx.x)	x.xx (x.xx, x.xx)	
No PLL Therapy ≤ {Median}	xxxx	(xx.x)	xx.x	xx.x (xx.x, xx.x)	xxx	(xx.x)	xx.x	xx.x (xx.x, xx.x)	x.xx (x.xx, x.xx)	
No PLL Therapy > {Median}	xxxx	(xx.x)	xx.x	xx.x (xx.x, xx.x)	xxx	(xx.x)	xx.x	xx.x (xx.x, xx.x)	x.xx (x.xx, x.xx)	

Table 4.1
Subgroup Analysis of Primary Composite Endpoint
(Protocol-defined ITT Population)

	EZ/Simva (N=xxxx)				Simva (N=xx xx)				Treatment Compariso n	
	n	(%) ‡	Annual % §	KM% (95% CI) ǁ	n	(%) ‡	Annual % §	KM% (95% CI) ǁ	HR (95% CI) ¶	p-Value ¶
Baseline HDL-C (mg/dL) ††										
≤ {Median}	xxxx	(xx.x)	xx.x	xx.x (xx.x, xx.x)	xxxx	(xx.x)	xx.x	xx.x (xx.x, xx.x)	x.xx (x.xx, x.xx)	x.xxx
> {Median}	xxxx	(xx.x)	xx.x	xx.x (xx.x, xx.x)	xxxx	(xx.x)	xx.x	xx.x (xx.x, xx.x)	x.xx (x.xx, x.xx)	

Baseline TG (mg/dL) ††										
≤ {Median}	xxx	(xx.x)	xx.x	xx.x (xx.x, xx.x)	xxx	(xx.x)	xx.x	xx.x (xx.x, xx.x)	x.xx (x.xx, x.xx)	x.xxx
> {Median}	xxx	(xx.x)	xx.x	xx.x (xx.x, xx.x)	xxx	(xx.x)	xx.x	xx.x (xx.x, xx.x)	x.xx (x.xx, x.xx)	
Baseline Non-HDL (mg/dL) ≤ {Median}	xxxx	(xx.x)	xx.x	xx.x (xx.x, xx.x)	xxxx	(xx.x)	xx.x	xx.x (xx.x, xx.x)	x.xx (x.xx, x.xx)	x.xxx
> {Median}	xxxx	(xx.x)	xx.x	xx.x (xx.x, xx.x)	xxxx	(xx.x)	xx.x	xx.x (xx.x, xx.x)	x.xx (x.xx, x.xx)	
Baseline hs-CRP (mg/L) ≤ 2	xxxx	(xx.x)	xx.x	xx.x (xx.x, xx.x)	xxxx	(xx.x)	xx.x	xx.x (xx.x, xx.x)	x.xx (x.xx, x.xx)	x.xxx
> 2	xxxx	(xx.x)	xx.x	xx.x (xx.x, xx.x)	xxxx	(xx.x)	xx.x	xx.x (xx.x, xx.x)	x.xx (x.xx, x.xx)	
REACH Risk Score										
{1st quartile}	xxxx	(xx.x)	xx.x	xx.x (xx.x, xx.x)	xxxx	(xx.x)	xx.x	xx.x (xx.x, xx.x)	x.xx (x.xx, x.xx)	x.xxx
{2nd quartile}	xxxx	(xx.x)	xx.x	xx.x (xx.x, xx.x)	xxxx	(xx.x)	xx.x	xx.x (xx.x, xx.x)	x.xx (x.xx, x.xx)	
{3rd quartile}	xxxx	(xx.x)	xx.x	xx.x (xx.x, xx.x)	xxxx	(xx.x)	xx.x	xx.x (xx.x, xx.x)	x.xx (x.xx, x.xx)	
{4th quartile}	xxxx	(xx.x)	xx.x	xx.x (xx.x, xx.x)	xxxx	(xx.x)	xx.x	xx.x (xx.x, xx.x)	x.xx (x.xx, x.xx)	

‡

Cruden number of events (

n) and percentage (%). § Annual % = total events/time at risk in year

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Hazard ratio (EZ/Simva vs. Simva), confidence interval, and p-Value for treatment-by-subgroup interaction from Cox proportional hazard model with covariates of the stratification factors (EARLY ACS trial, chronic prescription lipid-lowering experience, and high-risk ACS diagnosis), treatment, subgroup, and treatment-by-subgroup interaction. †† Subgroup is specified in the Statistical Analysis Plan.

N = Number of subjects in protocol-defined ITT population.

5. LDL-C BASELINE MEASUREMENTS FOR ANALYSIS

The Statistical Analysis Plan (SAP) specifies the baseline definition for lipids and lipoprotein as the last value in the pre-randomization period or randomization visit (Section 5.1.3). This baseline definition will be applied to change from baseline and percent change from baseline summaries in lipid parameters (LDL-C, HDL-C, Total-C, Non-HDL-C, TG, Apo B, Apo A-I, Lp(a), LDL-C:HDL-C, Total-C:HDL-C) and CRP as described in Section 5.1 of the SAP.

Based on the definition in the SAP, the baseline LDL-C value for the majority of subjects will be the central laboratory measurement on the day of randomization, rather than the qualifying LDL-C measurement taken at the local laboratory. The central lab measure may be lower than the local lab measure due to the recognized decrease in LDL-C that is typically observed following hospitalization for ACS. Therefore the central lab measure may not optimally reflect a subject's stable LDL-C value prior to an event, resulting in deflated absolute change from baseline values. In order to explore the differences in magnitude of response within treatment groups, change from baseline and percent change from baseline summaries will also be provided using the qualifying LDL-C measurement as a baseline.

The influence of prescription lipid-lowering therapy will also be explored by providing summaries of change from baseline in LDL-C by the stratification variable of lipid-lowering experience and by treatment group. Changes will be reported separately using both the qualifying LDL-C measurement and the LDL-C measurement on the day of randomization.

6. ANALYSIS OF LIPID AND CRP PARAMETERS

The Statistical Analysis Plan (SAP) specifies that the actual, change, and percent change from baseline in lipid parameters (LDL-C, HDL-C, Total-C, Non-HDL-C, TG, Apo B, Apo A-I, Lp(a), LDL-C:HDL-C, Total-C:HDL-C) and CRP will be summarized (N, mean, SD, median, IQR) by treatment group at each scheduled visit when applicable (Section 5.1). Also described in the SAP, a p-value for treatment difference will be provided based on a non-parametric approach using a one-way ANOVA model on the ranks extracting treatment effects (Section 5.1).

In addition to the summary statistics and non-parametric approach specified in the SAP, a longitudinal data analysis (LDA) method will be used to analyze the actual, change, and percent change from baseline in all lipid parameters with the exception of TG and Lp(a) at each scheduled visit and as a time-weighted average across visits. The mean response variables of interest for Simva vs. EZ/Simva will be compared using a parametric, longitudinal analysis of covariance (ANCOVA) model with factors for baseline lipid value, treatment, treatment-by-time interaction, baseline-by-time interaction, and stratification factors (participation in EARLY ACS trial, prescription lipid-lowering experience, and high-risk ACS diagnosis). Treatment group comparisons at each time point will be performed using an appropriate linear contrast from the ANCOVA model. In addition, the least-squares mean for each treatment and 95% confidence intervals will be estimated from the above ANCOVA model.

Due to the non-normal distribution associated with percent changes from baseline in TG, Lp(a), and CRP observed in prior studies, the data for these analyses will be transformed by the natural logarithm. A longitudinal ANCOVA model with factors for log transformed baseline value, treatment, treatment-by-time interaction, baseline-by-time interaction, and stratification factors will be used to analyze the log transformed actual values and change from baseline in log transformed values at each scheduled visit and as a time-weighted average across visits. Geometric means and geometric mean percent changes from baseline (expressed as [geometric mean – 1] x 100) in TG, Lp(a), and CRP levels will be calculated based on back-transformation via exponentiation of the model-based LS means. The treatment differences in geometric means and geometric mean percent changes from baseline will be calculated based on the difference in the back-transformed model-based LS means and 95% confidence intervals for the differences will be calculated using the delta method. Note that if after log transformation, there are severe departures from normality and a non-trivial amount of missing data, then a two- step approach will be implemented which will include multiple imputation (Rubin, 1987) of missing data followed by use of robust regression.

7. ADDITIONAL SAFETY ANALYSES

In addition to the protocol-defined ITT approach, safety parameters of serious AEs, CEC-adjudicated myopathy/rhabdomyolysis, LFT elevations, and CK elevations will also be analyzed as follows:

- Analysis similar to the protocol-defined ITT approach in the SAP, but excluding subjects who never took study drug.
- Analysis similar to the protocol-defined ITT approach in the SAP, but excluding subjects who never took study drug and limited to the time period when subjects are on- treatment up to and including 30 days after the last dose of study drug.

New onset of diabetes, which was not specified as a safety parameter of interest in the protocol, will also be summarized by treatment group. New onset will be defined as a subject with no prior history of diabetes, who had diabetes-related adverse events and/or received anti-diabetic medication post-randomization. Adverse events and serious adverse events for subjects with new onset of diabetes will be summarized by treatment group. Each of the approaches described above for the specified safety parameters will also be used for subjects with new onset of diabetes.

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8. ADDITIONAL ANALYSES RELATED TO MISSING DATA

Additional analyses will be performed on the primary composite endpoint to assess the influence of missing data on the treatment effect observed in the trial. Although the study is designed to follow all subjects until the end of the study, incomplete follow-up may occur when subjects withdraw consent or otherwise are lost to follow-up despite best efforts to obtain information. Blinded data will be utilized to inform on the quantity of missing data and observed event rates independent of treatment arm. Where possible, handling of missing data will attempt to follow the principles and recommendations of the National Academy of Sciences (NAS) report on the Prevention and Treatment of Missing Data in Clinical Trials. Publications on this topic in the New England Journal of Medicine will also be consulted (Ware NEJM 2012; 367(14): 1353-54 and Little NEJM 2012; 367(14): 1355-61).

Following is a brief description of the planned analyses:

Counting the *Number of patients* with missing follow-up data

Study close out visits are planned to start on May 1st, 2014. Any patient who cannot be contacted for the final visit on or after May 1st, 2014, has no outcome event as defined in the primary composite endpoint, and did not die while being actively followed will be considered as having missing follow-up. The number of patients with missing followup data will be summarized by treatment group.

Counting Missing *follow up time* for primary efficacy endpoint

Since the analysis of the primary endpoint is time to event analysis using Cox regression method, patients with missing follow-up data will be included in the analysis with time to event censored at the last visit date with full assessment of CV endpoints. While an accounting of the number of patients with missing follow-up data is helpful, a more accurate way to assess the impact of the missing data on the analysis results is to measure the amount of follow-up time lost for those patients because this quantifies the lost opportunity for further primary endpoint events. The lost follow-up time will be calculated as the time from the last visit with full assessment of CV endpoints to May 1st, 2014. The total amount of lost follow-up time will be summarized by treatment group and compared to the total potential follow-up time in a complete study where every patient is observed to have an primary outcome event, died while being actively followed, or followed-up until the end of study (on or after May 1st, 2104).

Multiple imputation analysis of lost follow-up time

Missing follow-up data on the primary endpoint will be simulated based on the assumption that the time to first primary event will have similar survival distribution pattern as the observed data. Parametric regression analysis will be used to estimate the survival curve using all the available follow-up data. Parametric distributions such as Weibull distribution and Exponential distribution will be explored to fit the distribution of the time to first primary efficacy event.

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Following scenarios will be explored on the hazard rate of the primary endpoint in missing follow-up data:

1. Missing completely at random (MCAR): missing follow up data in each treatment group have the same hazard rate as the observed data in the respective treatment group;

2. Missing at random (MAR): the missing follow up data from both treatment groups have the same hazard rate as the observed data from patients who were off treatment (treatment groups pooled);
3. Missing not at random (MNAR) and apply conservative controlled imputation:

   a. The missing follow up data from both treatment groups have the same hazard rate as the observed data from simvastatin monotherapy group (Reference Based approach);
   b. The between treatment group hazard ratio in the missing follow up data equals to the upper 95% confidence bound of the estimate from observed data and hazard rate in monotherapy group have the same hazard rate as the observed data (Delta Adjustment approach).
   c. Other data-driven delta adjustment approaches may also be explored to assess the degree of robustness of statistical significance of the observed treatment effect, such as:

      • The hazard rate in the monotherapy group with missing data will be fixed at the group's observed rate. The hazard rate in the experimental group with missing data will be varied over a range of values and will be compared to the hazard rate in the monotherapy group with missing data such that we can determine the point at which:

   o the overall (resulting from imputed + observed data) p-value of 0.01 is reached
   o the overall (resulting from imputed + observed data) p-value of 0.0394 (adjusted final p-value) is reached o an overall (resulting from imputed + observed data) hazard ratio of 1.0 is reached

The time-to-event analysis on the combined data (observed + projected/simulated) using the same Cox proportional hazard regression model for primary efficacy analysis will be performed. The same process of imputation and analysis will be repeated multiple times and the analysis results will then be summarized for empirical properties.

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To aid in the interpretation of the different multiple imputation strategies that will be investigated, the distribution of the number of imputed events will be summarized per treatment group for each strategy. Included in the descriptive summaries will be a histogram or kernel density plot with a discussion of a) how the distribution of imputed events varies across the imputation strategies, and b) how the imputed + observed event rate compares to the observed event rate.

Furthermore, if imbalances in missing follow-up data between the treatment groups and/ or among patient strata are observed, causes for the imbalances will be explored and additional analyses may be performed to address the potential bias introduced by the imbalanced missing data.

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9. GLOBAL RISK SCORE

The REACH score as defined by the Reduction of Atherothrombosis for Continued Health (REACH) Registry in the American Journal of Medicine (Vol 125, No 7, July 2012) will be used to define subgroups based on the risk for secondary cardiovascular events. Subgroup analyses based on the quartiles of the baseline REACH score will be performed for the primary efficacy endpoint.

In addition, two different global risk scores will be designed, one as a predictor of CV death, non- fatal MI, and stroke endpoints and another as a predictor of the IMPROVE-IT primary composite endpoint. Each global risk score will be developed separately, but using a similar algorithm. Using the Simvastatin treatment group alone (acting as the placebo in this trial), univariate analyses will be performed on a set of baseline risk factors to assess their association with these outcomes. Potentially important risk factors ($p \leq 0.05$) identified through the univariate analyses will be passed into the next stage. Multivariate analyses will then be conducted to identify a final predictive model. The regression coefficients from the model will be used to develop an integer-based global risk score.

The risk scores will be internally validated using the EZ/Simva treatment arm, in addition to using a technique such as bootstrapping. Discrimination will be evaluated to measure how well the model can separate subjects who did or did not have an event. In addition, calibration will be assessed to measure how well predicted probabilities agree with the actual observed results.

Following the development of the global risk scores, the effects of randomization to the Simvastatin/Ezetimibe treatment group in the quartiles of the risk scores will be examined for the entire subject population. Treatment effect will be assessed for the IMPROVE-IT primary composite endpoint and endpoints of CV death, non-fatal MI, and stroke.

10. CONTROLLING ALPHA FOR FINAL ANALYSIS

[Note: As the DSMB recommended that the trial continue after the 3rd interim analysis, the contents of this section (originally documented in February 2013) were no longer applicable at the time of the amended memo.]

As indicated in the Statistical Analysis Plan (Section 6), the DSMB asked for an additional review of the data (3rd interim analysis) which will be conducted in March of 2013. Although not explicitly stated in correspondence from the DSMB, it may be reasonable to assume that this review will include an unblinded analysis of efficacy data that would include early stopping of the trial for efficacy. The experiment-wise type I error accounting for interim analyses and a final analysis should the trial run until the full number of planned events (5250) occurs is controlled by the use of the Lan DeMets approximation to the O'Brien-Fleming alpha-spending function. In the event that the DSMB recommends stopping the trial for efficacy at the 3rd interim analysis, it is recognized that some "overrun" in events will occur following the interim analysis database lock, with additional endpoints accruing up to the time patients have a final study visit. The decision whether or not to stop the trial and the potential to commit a type I error under the null hypothesis of no treatment difference occurs and is controlled at the interim analysis. Therefore, the analysis including the overrun events serves not as a trial decision point, but only as an update to the interim analysis at which the trial stopped and as such does not contribute to the type I error. For this reason, should the trial stop at the 3rd interim analysis, estimation and analysis including the overrun events will use an unadjusted alpha level of 0.05.

11. ADDITIONAL EXPLORATORY ENDPOINTS

Several additional exploratory endpoints not pre-specified in the protocol will be analyzed:

- A composite endpoint of Cardiovascular death, non-fatal MI, or non-fatal stroke
- A composite endpoint of CHD death, non-fatal MI, or coronary revascularization with PCI or CABG ≥ 30 days after randomization
- A composite endpoint of Cardiovascular death or non-fatal MI
- A composite endpoint of CHD death or non-fatal MI

In addition, the primary and key secondary endpoints will be analyzed in a population similar to the protocol-defined ITT population in the SAP, but excluding subjects who never took study drug.

These analyses will be performed using methodology consistent with the IMPROVE-IT primary composite endpoint.

12. ON-TREATMENT ANALYSES

In addition to the protocol-defined intention-to-treat analysis (ITT) approach described in the Statistical Analysis Plan (Section 4), on-treatment analyses will be performed on the primary composite endpoint, key secondary composite endpoints, and tertiary endpoints. By study end, approximately half of the subjects will no longer be receiving study drug in the trial. Therefore on-treatment analyses may assist in understanding the treatment effect for subjects who remained on study drug.

All subjects who receive randomized treatment assignment and take study drug will be included in the analysis and analyzed using the actual treatment that they received. For each endpoint, the following analyses will be performed:

- Analysis of time to events censored at 30 days after the date of permanent discontinuation of study drug (primary approach).
- Analysis of time to events censored at 6 months after the date of permanent discontinuation of study drug.
- Analysis of time to events censored at 12 months after the date of permanent discontinuation of study drug.

The same statistical methodology (i.e., Cox proportional hazard model) used for the protocol-defined ITT analysis of the primary and key secondary endpoints will be used for the on-treatment analyses.

Note that by selecting subjects who were treated and excluding events based on discontinuation criteria, the randomization scheme is no longer maintained for the study. In addition, the choice of multiple time periods for which events are included in the analyses is subjective in nature. For these reasons, caution should be exercised in interpretation, as the results may be influenced by the bias introduced by performing nonrandomized comparisons as well as the element of unaccounted for multiplicity.

13. PROTOCOL-DEFINED INTENTION-TO-TREAT POPULATION

The intent-to-treat (ITT) population defined in the protocol is not a true ITT population (i.e., all patients included in their randomized treatment group regardless of actual treatment received). The purpose of this section is to provide an operational definition of the protocol-defined ITT population that is also documented in a memo from 9/14/2014 titled "MK-0653A IMPROVE-IT Study (SCH465981 P04103): Implementation of Protocol-Defined ITT Population". The ITT population is defined in the protocol as:

8.1 Data Sets

The intent-to-treat (ITT) population includes all subjects who receive randomized treatment assignment. Specifically, all subjects who receive randomized treatment assignment but never take study drug will be analyzed using the assigned treatment. All other subjects will be analyzed using the actual treatment that they received. Subjects with protocol deviations or violations will be analyzed in the ITT population. All the safety and efficacy data will be analyzed based on the ITT population.

The following rules will be used to assign protocol-defined ITT treatment group:

- Use the randomized treatment group if subject took at least one dose of study drug to which subject was randomized, even if the subject took incorrect study drug at some other point in the study
- Use the randomized treatment group if subject never took study drug
- Assign the other treatment group (i.e., not the treatment group to which subject was randomized) if subject took incorrect study drug for their entire time on treatment in the trial

Immediately after unblinding of the database DCRI will identify subjects who took incorrect study drug for the entire trial and send the list of subjects to Merck and TIMI. The memo referenced above will be updated to include the subject ID numbers, randomized treatment group, and protocol-defined ITT assignment based on the list from DCRI. Based on a blinded review of the data it is anticipated that number of affected subjects will be very small, but a true ITT analysis of the primary and 3 key secondary endpoints will be performed as a sensitivity analysis.

14. CLINICAL ENDPOINTS AFTER THE FINAL STUDY VISIT

The protocol dictates that a subject is considered to have completed the study upon the completion of the last protocol-specified visit or contact. Clinical endpoint events were to be collected up to a subject's final study visit, which was operationally set to be on or after May 1st, 2014. In the event that endpoints are spontaneously reported to investigator sites after a subject's final study visit, the endpoints will be sent for adjudication by the CEC and entered into the database. Events that were adjudicated to occur after the final study visit will not be included in any pre-specified analyses. These events will be provided as a separate listing.

15. DOCUMENT REVISION HISTORY

Date	Summary of Major Changes
February 28, 2013	Original Document
October 15, 2014	• Section 2: Added clarification of recurrent events analysis. • Section 8: Included additional details on analyses related to missing data. • Section 9: Added REACH score. • Section 12: Included description of on-treatment analyses to be conducted on the primary composite endpoint and three key secondary composite endpoints. • Section 13: Added description of operational definition for protocol-defined ITT population. • Section 14: Added description of handling of clinical endpoints reported after the final study visit.